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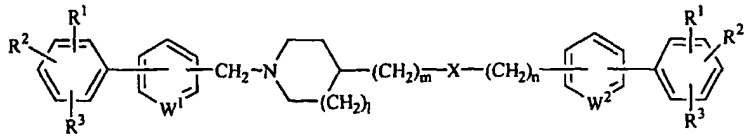
(54) Title: MEDICINE FOR TREATING CANCER



(I)

(57) Abstract: Abstract The present invention is directed to a method for treating cancer, a method for inhibiting histone deacetylase, and a method for facilitating gene therapy, comprising administering an effective amount of a cyclic amine compound represented by the following formula (1):(wherein R1, R2, and R3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W1 and W2, which are identical to or different from each other, represent N or CH; X represents O, NR4, CONR4, or NR4CO; R4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a hydrate thereof.208

WO 03/086397 A1

Description

Medicine for Treating Cancer

Technical Field

The present invention relates to a medicine for treating cancer with reduced side effects.

Background Art

Trichostatin A (hereinafter referred to as "TSA") was first isolated as an antifungal antibiotic from *Streptomyces hygroscopicus* by Tsuji and others in 1976 (J. Antibiot. (Tokyo), 1976 29(1): 1-6). Later, Yoshida and others reported that TSA is a potent inducer of differentiation in erythroleukemia cells (Cancer Res., 1987 47(14): 3688-91) and also acts as an inhibitor in G1 and G2 phases in the cell cycle (Exp. Cell. Res., 1988 177(1): 122-31), and also clarified that these actions are caused by inhibiting histone deacetylase (hereinafter referred to as "HDAC") (J. Biol. Chem., 1990 265(28): 17174-9). It has been suggested that TSA inhibits HDAC by formation of a stable complex from the hydroxamic acid moiety in TSA structure and the amino acid in the active center of HDAC which are chelated via metallic zinc (Nature, 1999 401(6749): 188-93).

HDAC inhibition causes highly acetylated nuclear histones, which leads to expression of genes. Among the genes affected by inhibition of HDAC, quite a few are important ones having close relation with cancer. Therefore, a number of HDAC inhibitors have been studied for their potential use as an anticancer agents. Some actions of HDAC inhibitors include inhibition of proliferation, acceleration of differentiation, apoptosis induction, upraising of p21 expression, and upraising of MHC expression. Moreover, by virtue of gene expression promoting action of HDAC, they are expected to improve the efficacy of transferred genes in gene therapy (see, for example, "*Ketsueki · Shuyo-ka*," 2001 42(5): 416-22; Gene & Medicine, 2002 6(1): 10-14; Japanese Application Laid-Open (*kokai*) No. 2000-256397).

Anticancer actions of HDAC inhibitors, particularly TSA, reported heretofore includes proliferation inhibition against cultured stomach cancer cells and oral cancer

cells (Int. J. Cancer, 2000 88(6): 992-7); carcinostatic action against a rat breast cancer model (Clin. Cancer Res., 2001 7(4): 971-6); and proliferation inhibition and apoptosis induction for cultured liver cancer cells (J. Hepatol., 2002 36(2): 233-40).

Studies on HDAC inhibitors, which are expected to serve as anti-cancer drugs or to facilitate gene therapies, have focused on the synthesis of analogues of acetyl lysine, which acts as a substrate of HDAC. That is, a variety of HDAC inhibitors having a functional group which interacts with zinc (e.g., a hydroxamic acid group or an epoxy-ketone group) and those having a cap site consisting of an aromatic or cyclic peptide have been synthesized and studied. In addition, as a peptide not having an analogous structure of acetyl lysine as described above, FK228 and the like have been synthesized and studied as HDAC inhibitors ("*Ketsueki・Shuyo-ka*," 2001 42(5): 416-22).

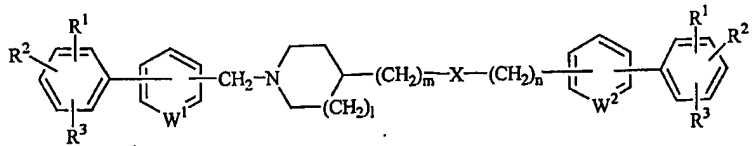
However, thus far HDAC inhibitors which are non-peptide compounds and are not analogues of acetyl lysine have virtually remained unknown.

Thus, the present invention provides a novel substance which inhibits HDAC and which is a non-peptide and is not an analogue of HDAC substrate; and a method for treating cancer using the substance with reduced side effects.

Disclosure of the Invention

Accordingly, by use of culture cell systems, the present inventors have searched for substances which affect HDAC, and quite unexpectedly have found that compounds represented by the following formula (1) exhibit excellent HDAC-inhibitory activity, gene therapy facilitating effect, and cancer cell proliferation-inhibiting action, and thus are useful medicines for treating cancer to complete the invention.

Accordingly, the present invention provides a medicine for treating cancer, comprising administering an effective amount of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen-substituted alkyl group, an alkoxy group, an alkylthio group, a carboxy group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a hydrate thereof.

The present invention also provides a method for inhibiting HDAC, comprising administering an effective amount of the cyclic amine compound represented by the above formula (1), a salt thereof, or a hydrate thereof.

The present invention also provides a method for facilitating gene therapy, comprising administering an effective amount of a cyclic amine compound represented by the above formula (1), a salt thereof, or a hydrate thereof.

The present invention also provides a medicine for treating cancer and an HDAC inhibitor, comprising, as an active ingredient, a cyclic amine compound represented by the above formula (1), a salt thereof, or a hydrate thereof.

The present invention also provides use of a cyclic amine compound represented by the above formula (1), a salt thereof, or a hydrate thereof for producing a medicine for treating cancer and an HDAC inhibitor.

The present invention also provides a medicinal composition for treating cancer and an HDAC inhibiting composition, comprising a cyclic amine compound represented by the above formula (1), a salt thereof, or a hydrate thereof, and a pharmaceutically acceptable carrier.

Brief Description of the Drawings

Fig. 1 shows correlation in terms of various gene expression level.

Fig. 2 shows relative gene expression levels of several genes.

Best Mode for Carrying Out the Invention

Examples of the halogen atom represented by R^1 to R^3 in formula (1) include a

fluorine atom, a chlorine atom, a bromine atom, and an iodine atom.

Examples of the alkyl group represented by R^1 to R^4 include linear, branched, or cyclic C1-C8 alkyl groups. Examples of the linear or branched C1-C8 alkyl groups include a methyl group, an ethyl group, a propyl group, a butyl group, a pentyl group, a hexyl group, a heptyl group, and an octyl group. Examples of the cyclic C3-C8 alkyl groups include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cyclohexylmethyl group, and a cyclohexylethyl group. Of these, C1-C6 alkyl groups such as a methyl group, an ethyl group, a n-propyl group, an isopropyl group, and a n-butyl group are particularly preferred.

Examples of the halogen-substituted alkyl group represented by R^1 to R^3 include C1-C8 alkyl groups substituted by one to three halogen atoms. Of these, C1-C6 alkyl groups substituted by one to three halogen atoms such as a trifluoromethyl group and a 2,2,2-trifluoroethyl group are particularly preferred.

Examples of the alkoxy group include linear, branched, or cyclic C1-C8 alkoxy groups. Examples of the linear or branched C1-C8 alkoxy groups include a methoxy group, an ethoxy group, a n-propoxy group, an iso-propoxy group, a n-butoxy group, an iso-butoxy group, a sec-butoxy group, a tert-butoxy group, a pentyloxy group, and a hexyloxy group. Examples of the C3-C8 cycloalkyloxy groups include a cyclopropyloxy group, a cyclobutyloxy group, a cyclopentyloxy group, a cyclohexyloxy group, a cyclohexylmethyloxy group, and a cyclohexylethyloxy group. Of these, a C1-C6 alkoxy group such as a methoxy group, an ethoxy group, a n-propoxy group, an isopropoxy group, or a n-butoxy group is particularly preferred.

Examples of the alkylthio group include C1-C8 alkylthio groups, and C1-C6 alkylthio groups such as a methylthio group, an ethylthio group, a n-propylthio group, and an isopropylthio group are preferred.

Examples of the alkoxycarbonyl group include C1-C6 alkoxycarbonyl groups, and C1-C4 alkoxycarbonyl groups such as a methoxycarbonyl group, an ethoxycarbonyl group, and a tert-butoxycarbonyl group are preferred.

Examples of the alkanoyl group include C1-C6 alkanoyl groups, and C1-C4 alkanoyl groups such as an acetyl group, a propionyl group, a butyryl group, and an iso-butyryl group are preferred.

Examples of the alkenyl group represented by R^4 include C3-C8 alkenyl

groups, and C3-C6 alkenyl groups such as a 2-propenyl group and a 3-butenyl group are preferred. Examples of the alkynyl group include C3-C8 alkynyl groups, and C3-C6 alkynyl groups such as a 2-propynyl group and a 3-butynyl group are preferred.

Examples of the aryl group represented by R^4 include C6-C14 aryl groups, and, among others, a phenyl group, a naphthyl group, an anthryl group, an indenyl group, an indanyl group, and a 5,6,7,8-tetrahydronaphthyl group are preferred.

Examples of the heteroaryl group represented by R^4 include heteroaryl groups containing a 5- or 6-membered ring having one to four nitrogen atoms, and among others, an imidazolyl group, a pyridyl group, and a pyrimidinyl group are preferred. Examples of the aralkyl group represented by R^4 include a (C6-C14)-aryl-(C1-C6)-alkyl group, and a phenyl-(C1-C6)-alkyl group or a naphthyl-(C1-C6)-alkyl group such as a benzyl group, a naphthylmethyl group, a phenylethyl group, or a phenylpropyl group is exemplified. Examples of the heteroaralkyl group represented by R^4 include heteroaryl-(C1-C6)-alkyl groups containing a 5- or 6-membered ring having one to four nitrogen atoms such as an imidazolyl-(C1-C6)-alkyl group, a pyridyl-(C1-C6)-alkyl group, or a pyrimidinyl-(C1-C6)-alkyl group.

The aforementioned aryl groups, heteroaryl groups, aralkyl groups, or heteroaralkyl groups may be substituted by a substituent. Examples of the substituent include one to three groups or atoms selected from an alkyl group, an alkoxy group, a halogen-substituted alkoxy group, an alkylthio group, an alkylsulfinyl group, an alkylsulfonyl group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group. Examples of the alkyl group, the alkoxy group, and the alkylthio group include those described in relation to the R^1 to R^3. Examples of the alkyl group contained in the alkylsulfinyl group and the alkylsulfonyl group include a C1-C3-alkyl group, particularly a methyl group, an ethyl group, a n-propyl group, and an isopropyl group. Preferable examples of the halogen-substituted alkoxy group include a C1-C8 alkoxy group substituted by one to three halogen atoms, particularly a C1-C4 alkoxy group substituted by one to three halogen atoms such as a trifluoromethoxy group or a 2,2,2-trifluoroethoxy group. Examples of the alkylenedioxy group include a C1-C3 alkylenedioxy group such as a methylenedioxy group, an ethylenedioxy group, or a propylenedioxy group.

X is preferably NR^4, and R^4 is more preferably a C1-C8 alkyl group, a substituted or unsubstituted C6-C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5- or 6-membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6-C14)-aryl-(C1-C6)-alkyl group, or a substituted or unsubstituted heteroaryl-(C1-C6)-alkyl group containing a 5- or 6-membered ring having one to four nitrogen atoms.

Preferably, R^1, R^2, and R^3 are bonded at the 3-, 4-, and 5-positions, respectively, of the phenyl group. In this case, more preferably, R^1 and R^3 (i.e., the groups bonded at the 3- and 5-positions of the phenyl group) are an alkoxy group or a halogen atom, and R^2 (i.e., the group bonded at the 4-position of the phenyl group) is a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen-substituted alkyl group, an alkoxy group, an alkylthio group, a carboxy group, an alkoxycarbonyl group, or an alkanoyl group.

l is a number of 0 or 1, with 1 being preferred.

W^1 is preferably N. W^2 is preferably N.

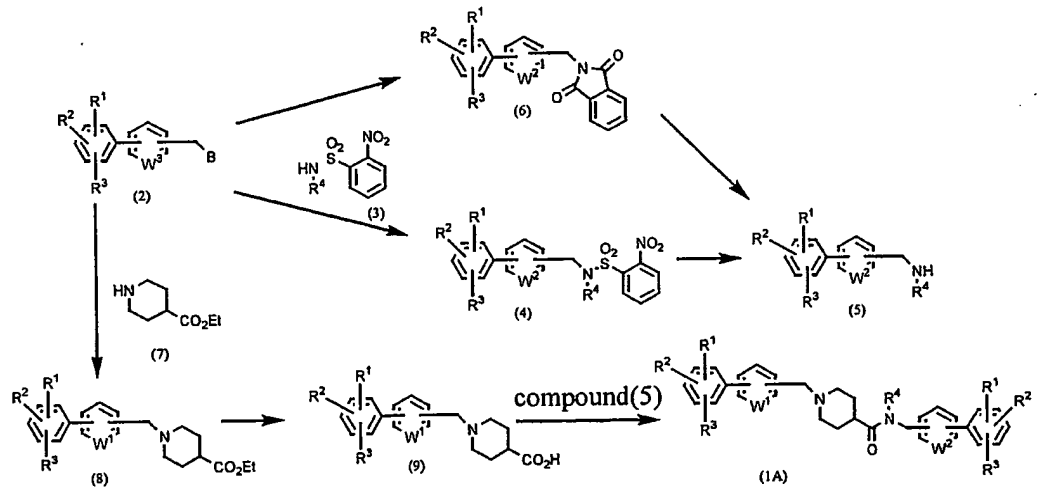
Among the compounds represented by formula (1), preferred is a compound in which X is NR^4, and R^4 is a C1-C8 alkyl group, a substituted or unsubstituted C6-C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5- or 6-membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6-C14)-aryl-(C1-C6)-alkyl group, or a substituted or unsubstituted heteroaryl-(C1-C6)-alkyl group containing a 5- or 6-membered ring having one to four nitrogen atoms. More preferably, R4 is a phenyl group or a pyridyl group which may be substituted by one or two groups or atoms selected from a halogen atom, an alkyl group, an alkoxy group, an alkylthio group, a trifluoromethyl group, and an alkylenedioxy group, or a C1-C8 alkyl group.

No particular limitations are imposed on the acid-addition salts of the compound (1) of the present invention, so long as the salts are pharmaceutically acceptable. Examples of the salts include addition salts of mineral acids such as hydrochlorides, hydrobromides, hydriodides, sulfates, and phosphates; and addition salts of organic acids such as benzoates, methanesulfonates, ethanesulfonates, benzenesulfonates, *p*-toluenesulfonates, oxalates, malates, fumarates, tartarates, citrates, and acetates.

The compound (1) of the present invention may form a solvate represented by hydrate, and the present invention encompasses such solvates.

The compound (1) of the present invention can be produced through the following methods A through L.

Process A: Preparation of the compound of the formula (1) wherein l = 1, m =0, n=1 and X=CONR^4



wherein, W^1, W^2 , R^1, R^2, R^3 and R^4 are as defined above, W^3 has the same meaning as W^1 or W^2, and B denotes a leaving group such as a halogen atom, or methanesulfonyloxy or p-toluenesulfonyloxy group.

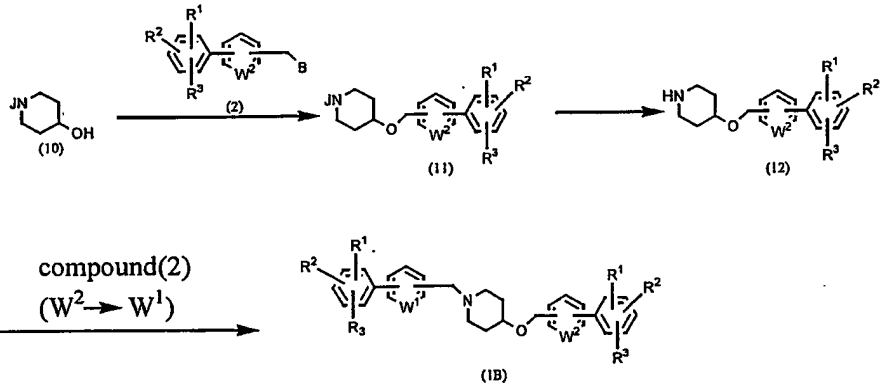
Compound (2) and a N-(2-nitro)benzenesulfonylamine derivative (3) are reacted to give compound (4). The resulting compound (4) is treated with thiophenol in the presence of a base such as potassium carbonate to eliminate the 2-nitrobenzenesulfonyl group, thereby giving amine compound (5). Alternatively, when R^4 is H, it is possible to react compound (2) with potassium phthalimide and then treat the resulting phthalimide derivative (6) with hydrazine to give the corresponding amine compound (5).

On the other hand, compound (2) is reacted with ethyl isonipecotate (7) in a solvent such as acetonitrile, N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), tetrahydrofuran (THF), dioxane, toluene, benzene, etc. in the presence of a

base such as potassium carbonate or the like at a temperature between 0℃ and a reflux temperature for several hours to several days, preferably at room temperature overnight, to give compound (8). The compound (8) is subjected to a usual alkaline hydrolysis to give the corresponding carboxylic acid compound (9).

The carboxylic acid compound (9) is reacted with the amine compound (5) using a dehydration condensing agent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (water-soluble carbodiimide), 2-(1H-benzotriazol -1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) or the like in a solvent such as chloroform, dichloroethane, THF, dioxane, acetonitrile, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 12 hours, to give an end product (1A).

Process B: Preparation of the compound of the formula (1) wherein l = 1, m =0, n=1 and X=O

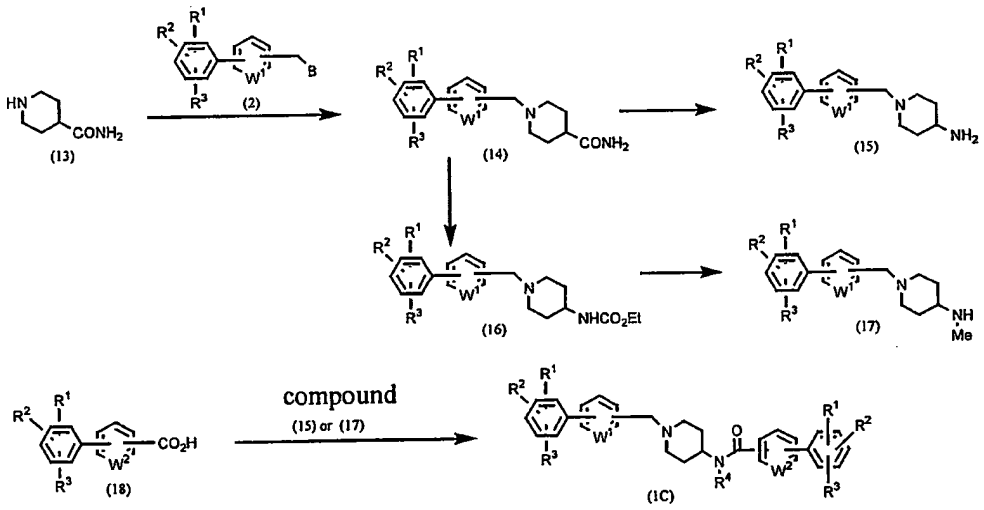


wherein, B, W^1, W^2 , R^1, R^2 and R^3 are as defined above, and J denotes a protecting group such as benzyloxycarbonyl, tert-butoxycarbonyl, acetyl, benzoyl or benzyl group. Incidentally, in the reaction schemes shown above and below, the expression "(W^2→ W^1)" following the term "compound(2)" means that W^2 in the formula representing compound (2) is changed to W^1.

4-hydroxypiperidine compound (10) with a protected amino group is reacted with compound (2) in the presence of sodium hydride and potassium iodide in a solvent such as DMF, DMSO, etc. at a temperature between 0°C and a reflux

temperature for several hours to several days, preferably at room temperature for 2 days, to give compound (11). The protecting group in the compound (11) is removed in a known manner. The resulting compound (12) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give an end product (1B).

Process C: Preparation of the compound of the formula (1) wherein l = 1, m =0, n=0, X=NR^4CO and R^4=H or Me



wherein, B, W^1, W^2, R^1, R^2 and R^3 are as defined above, and R^4 denotes a hydrogen atom or methyl group.

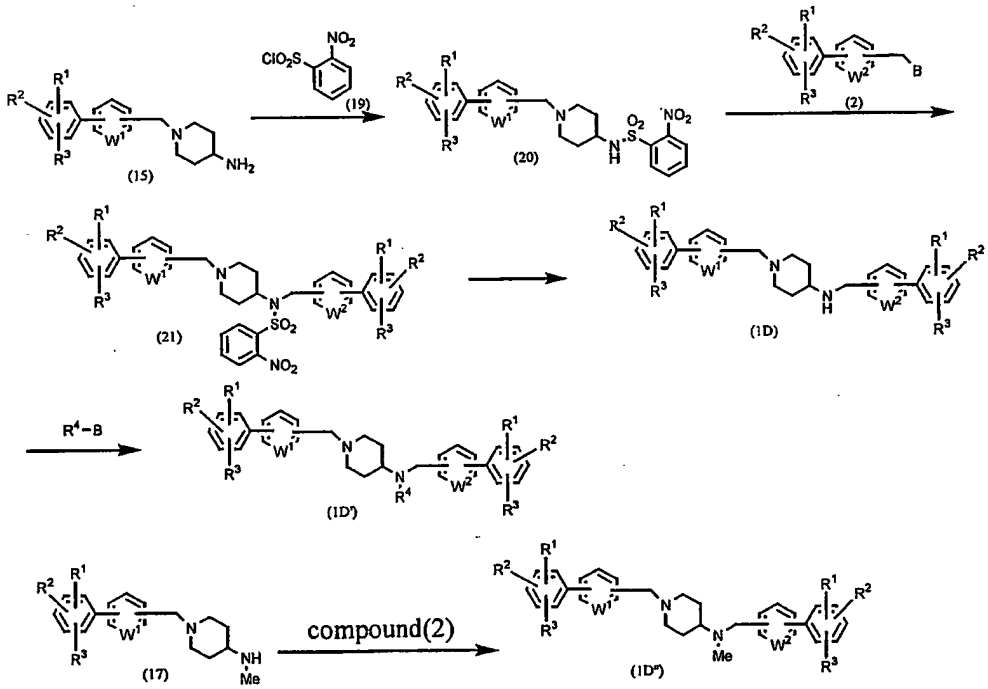
Isonipecotamide (13) is reacted with compound (2) in the presence of a base such as potassium carbonate, sodium carbonate or the like in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (14). The compound (14) is subjected to Hofmann rearrangement reaction to give amine compound (15).

On the other hand, by subjecting the compound (14) to Hofmann rearrangement reaction in ethanol, carbamate compound (16) is obtained. Then, by subjecting the

compound (16) to a reduction reaction using lithium aluminum hydride, methylamine compound (17) is obtained.

By reacting carboxylic acid compound (18) with the amine compound (15) or methylamine compound (17) similarly to the condensation reaction in Process A, an end compound (1C) is obtained.

Process D: Preparation of the compound of the formula (1) wherein l = 1, m =0, n=1 and X=NR^4



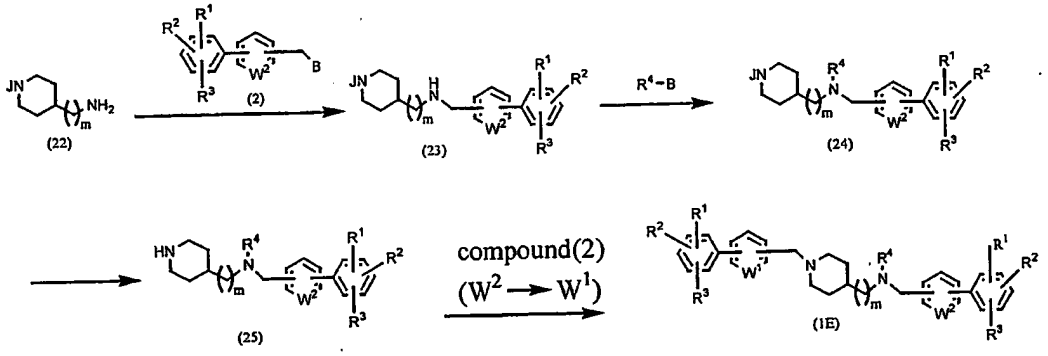
wherein, B, W^1, W^2, R^1, R^2 and R^3 are as defined above, and R^4 denotes an alkyl, alkenyl, alkynyl, aralkyl or heteroaralkyl group.

The amine compound (15) mentioned in the above is reacted with 2-nitrobenzenesulfonyl chloride (19) according to a known manner to give compound (20). The compound (20) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (21). The benzenesulfonyl group of the compound (21) is removed similarly to the procedure for

the compound (4) in Process A to give an end compound (1D) (R^4=H). The compound (1D) is reacted with R^4-B in the presence of a base such as sodium carbonate, sodium bicarbonate, potassium carbonate, cesium carbonate or the like in a solvent such as acetonitrile, THF, dioxane, chloroform, dichloromethane, DMF, DMSO or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at 80°C for 12 hours, to give compound (1D').

On the other hand, the methylamine compound (17) is reacted compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give an end compound (1D") (R^4=Me).

Process E: Preparation of the compound of the formula (1) wherein l = 1, m =0 or 1, n=1 and X=NR^4,

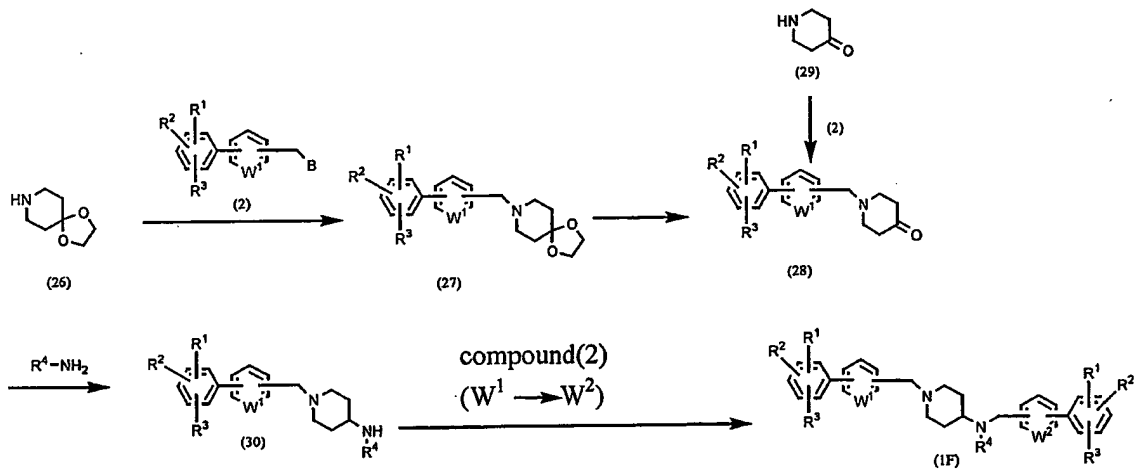


wherein, B, J, W^1, W^2 , R^1, R^2 and R^3 are as defined above, and R^4 denotes an alkyl, alkenyl, alkynyl, aralkyl or heteroaralkyl group.

Aminopiperidine derivative (22) in which the amino group on the ring is protected is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (23). The compound (23) is reacted with R^4-B in the presence of a base such as sodium carbonate, sodium

bicarbonate, potassium carbonate, cesium carbonate or the like in a solvent such as acetonitrile, THF, dioxane, chloroform, dichloroethane, DMF, DMSO or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at 80°C for 12 hours, to give compound (24). After removal of the protecting group, the compound (25) is reacted compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (1E).

Process F: Preparation of the compound of the formula (1) wherein l = 1, m =0, n=1 and X=NR^4,



wherein, B, W^1, W^2 , R^1, R^2 and R^3 are as defined above, and R^4 denotes an alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, aryl or heteroaryl group.

4-piperidone ethylene ketal (26) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (27), which in turn is deketalized by using an acid to give ketone compound (28).

On the other hand, 4-piperidone (29) is reacted compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO,

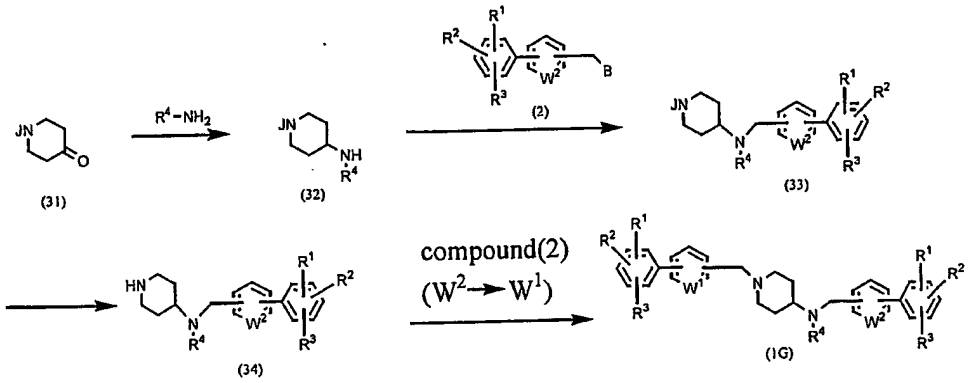
THF, dioxane or the like at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (28). Using the compound (28), amine compound (30) can be prepared according to either of the following two synthesis processes:

Synthesis process 1: The compound (28) is reacted with an amine compound of the formula: R^4-NH_2 in the presence of molecular sieves in toluene or benzene at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at reflux temperature for 12 hours, followed by reaction with a reducing agent such as sodium borohydride or sodium cyanoborohydride at a temperature between 0°C and a reflux temperature for several minutes to several days, preferably at room temperature for 1 hour, to give the amine compound (30).

Synthesis process 2: The compound (28) is reacted with an amine compound of the formula: R^4-NH_2 in the presence of a reducing agent such as sodium triacetoxy boron hydride in a solvent such as dichloromethane, 1,2-dichloroethane, methanol, ethanol, etc. at a temperature between 0°C and a reflux temperature for several minutes to several days, preferably at room temperature for 4 hours, to give the amine compound (30).

The resulting compound (30) is reacted compound (2) in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give an end product (IF).

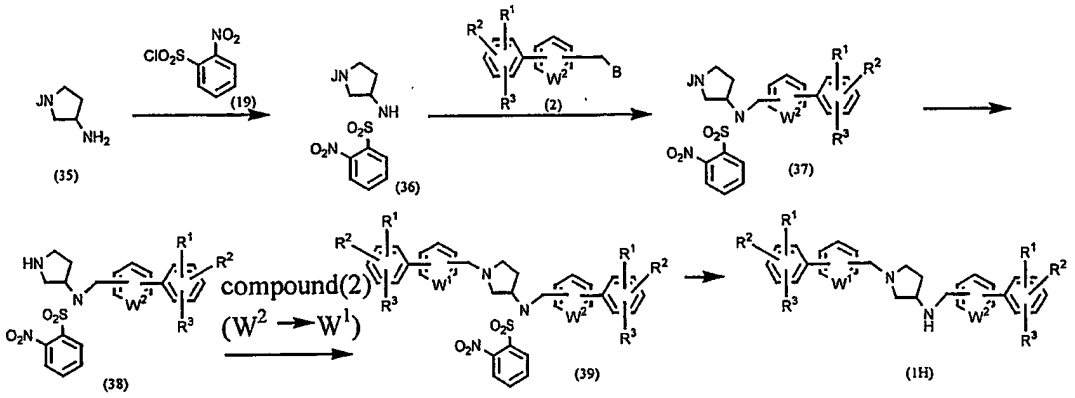
Process G: Preparation of the compound of the formula (1) wherein l = 1, m =0, n=1 and X=NR^4



wherein, B, J, W^1, W^2 , R^1, R^2 and R^3 are as defined above, and R^4 denotes an alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, aryl or heteroaryl group.

4-piperidone derivative (31) in which the amino group on the ring is protected is reacted with an amine compound R^4-NH_2 similarly to the procedure for preparation of compound (30) in Process F to give compound (32). The compound (32) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (33). After removal of the protecting group from the compound (33), the resulting compound (34) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give an end product (1G).

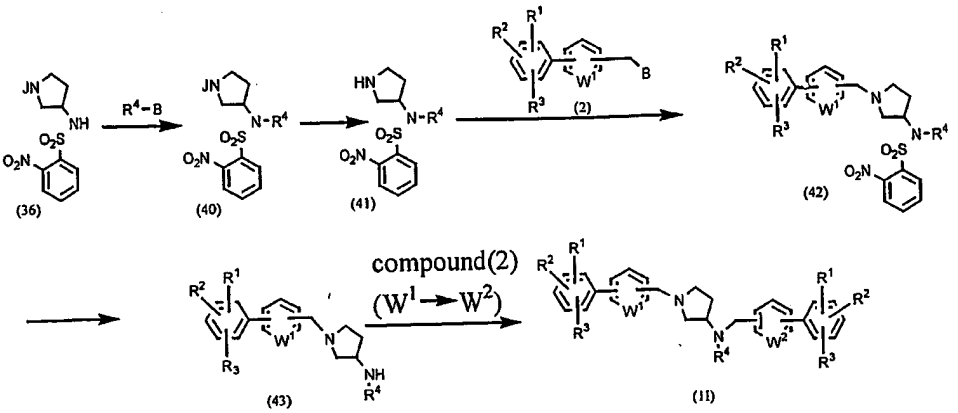
Process H: Preparation of the compound of the formula (1) wherein l = 0, m =0, n=1 and X=NH



wherein, B, J, W^1, W^2 , R^1, R^2 and R^3 are as defined above.

3-aminopyrrolidine derivative (35) with a protected amino group on the ring is reacted with 2-nitrobenzenesulfonyl chloride (19) under usual conditions to give a benzenesulfonyl derivative (36). The derivative (36) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (37). The protecting group of the amino group is removed from the compound (37) to give compound (38), which in turn is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, , DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (39). By subjecting the compound (39) to a reaction similar to that in the preparation of compound (5) in Process A, an end product (1H) is obtained.

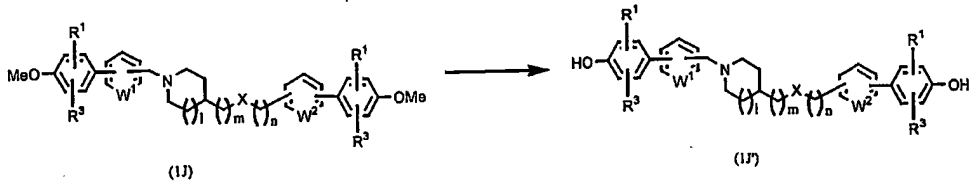
Process I: Preparation of the compound of the formula (1) wherein l = 0, m =0, n=1 and X=NR^4



wherein, B, J, W^1, W^2 , R^1, R^2 and R^3 are as defined above, and R^4 denotes an alkyl, alkenyl, alkynyl or aralkyl group.

Compound (36) is reacted with R^4-B in the presence of a base such as sodium carbonate, potassium carbonate, etc. in a solvent such as acetonitrile, THF, dioxane, chloroform, dichloroethane, DMF, DMSO, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at 80°C for 12 hours, to give compound (40). The amino-protecting group is removed from the compound (40), and the resulting compound (41) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0℃ and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give compound (42). By subjecting the compound (42) to a reaction similar to that in the preparation of compound (5) in Process A, compound (43) is obtained. The compound (43) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0℃ and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give an end product (1I).

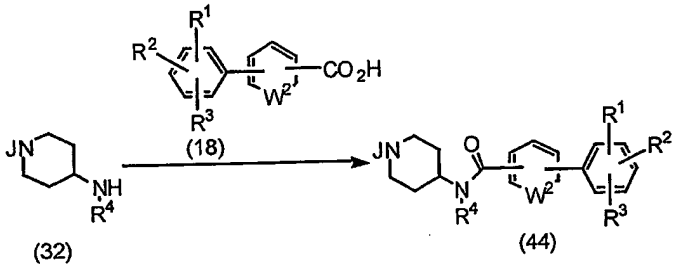
Process J: Preparation of the compound of the formula (1) wherein R^2=OH

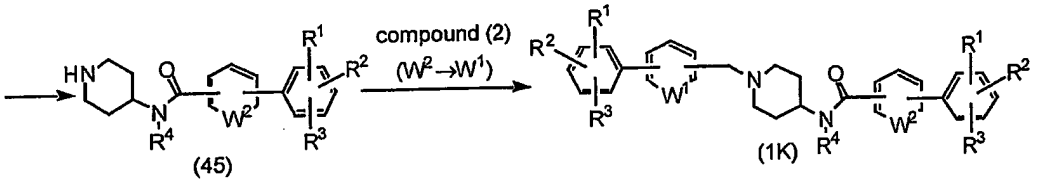


wherein, X, W^1, W^2 , R^1, R^3, l, m and n have the same meanings as initially defined.

By reacting methoxy compound (1J) with iodotrimethylsilane in a solvent such as toluene, benzene, chloroform, dichloromethane, etc. at a temperature between -25°C and a reflux temperature for several minutes to several days, preferably at 0°C for 2 hours, there can be obtained an end product (1J').

Process K: Preparation of the compound of the formula (1) wherein l = 1, m = 0, n = 0 and X = NR^4CO

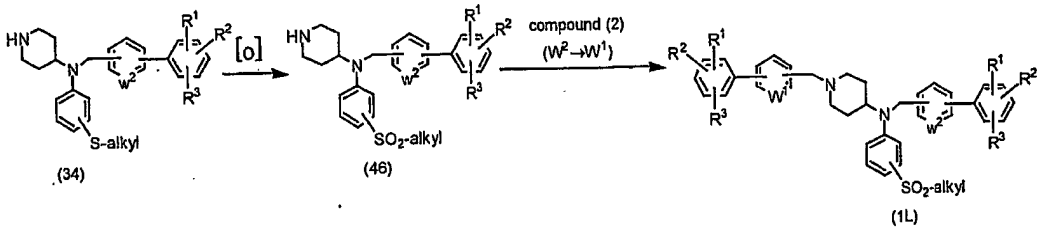




wherein, B, J, W^1, W^2, R^1, R^2 and R^3 are as defined above, and R^4 denotes an alkyl, alkenyl, alkynyl, aralkyl, heteroaralkyl, aryl or heteroaryl group.

Compound (32), which is described in the Process G, is reacted with compound (18) in the similar procedure as described in the preparation of compound (1A) in Process A to give gompound (44). After removal of the protecting group from the compound (44), the resulting compound (45) is reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at room temperature for 4 hours, to give an end product (1K).

Process L: Preparation of the compound of the formula (1) wherein l=1, m=0, n=1 and X= alkylsulfonylphenylamino group



wherein, B, W^1, W^2, R^1, R^2 and R^3 are as defined above.

Compound (34), which was prepared in the Process G (wherein X denotes alkylthiophenylamino group), is reacted with an oxdation agent such as 3-chloroperbenzoic acid, peracetic acid, hydrogen peroxide, etc. in the known manner to give an alkylsulfonyl derivative (46). Compound (46) is then reacted with compound (2) in the presence of a base such as potassium carbonate in a solvent such as acetonitrile, DMF, DMSO, THF, dioxane, etc. at a temperature between 0°C and a reflux temperature for several hours to several days, preferably at 70°C overnight, to give an end product (1L).

The compounds (1) according to the present invention are obtained by any of the above-described processes and may further be purified by using an ordinary purification means such as recrystallization or column chromatography as needed. As needed, the compounds may also be converted into the desired salts or solvates in a method known *per se* in the art. When the compounds (1) have an asymmetric carbon atom, the present invention includes any configurational isomers.

These compounds (1) according to the present invention possess the almost same profile of gene expression in human cells as TSA which has the HDAC inhibiting action, and exhibit potent growth inhibitory effect on cultured human cancer cells as shown in the test example.

The medicine for treating cancer according to the present invention comprises a compound (1), a salt thereof, or a solvate thereof as an active ingredient. The form of administration may be suitably selected as necessary for the therapeutic application intended without any particular limitation, including oral preparations, injections, suppositories, ointments, inhalants, eye drops, nose drops and plasters. A composition suitable for use in these administration forms can be prepared by blending a pharmaceutically acceptable carrier in accordance with the conventional preparation

method publicly known by those skilled in the art.

When an oral solid preparation is formulated, an excipient, and optionally, a binder, disintegrator, lubricant, colorant, a taste corrigent, a smell corrigent and the like are added to compound (1) and the resulting composition can be formulated into tablets, coated tablets, granules, powders, capsules, etc. in accordance with methods known in the art.

As such additives described above, any additives may be used which are generally used in the pharmaceutical field. Examples include excipients such as lactose, sucrose, sodium chloride, glucose, starch, calcium carbonate, kaolin, microcrystalline cellulose and silicic acid; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl starch, methyl cellulose, ethyl cellulose, shellac, calcium phosphate and polyvinyl pyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, sodium hydrogencarbonate, calcium carbonate, sodium lauryl sulfate, monoglyceryl stearate and lactose; lubricants such as purified talc, stearic acid salts, borax and polyethylene glycol; and taste corrigents such as sucrose, orange peel, citric acid and tartaric acid.

When an oral liquid preparation is formulated, a taste corrigent, buffer, stabilizer, smell corrigent and/or the like are added to compound (1) and the resulting composition can be formulated into internal liquid preparations, syrup preparations, elixirs, etc. in accordance with methods known in the art. In this case, vanillin as the taste corrigent, may be used. As the buffer, sodium citrate may be mentioned. As examples of the stabilizer, tragacanth, gum arabic and gelatin may be mentioned.

When an injection is formulated, a pH adjustor, buffer, stabilizer, isotonicity agent, local anesthetic and the like may be added to compound (1) according to the present invention, and the resultant composition can be formulated into subcutaneous, intramuscular and intravenous injections in accordance with methods known in the art. Examples of the pH adjustor and buffer in this case include sodium citrate, sodium acetate and sodium phosphate. Examples of the stabilizer include sodium pyrosulfite, EDTA, thioglycolic acid and thiolactic acid. Examples of the local anesthetic include procaine hydrochloride and lidocaine hydrochloride. Examples of the isotonicity agent include sodium chloride and glucose.

When a suppository is formulated, a carrier preparation known in the art, for example, polyethylene glycol, lanoline, cacao butter, fatty acid triglyceride or the like, and optionally, a surfactant such as Tween (trade mark) and the like are added to the compound (1), and the resultant composition can be formulated into suppositories in accordance with methods known in the art.

When an ointment is formulated, a base material, stabilizer, wetting agent, preservative and the like, which are generally used, are blended with compound (1) as needed, and the resulting blend is mixed and formulated into ointments in accordance with known methods. Examples of the base material include liquid paraffin, white vaseline, bleached beeswax, octyldodecyl alcohol and paraffin. Examples of the preservative include methyl p-hydroxybenzoate, ethyl p-hydroxybenzoate and propyl p-hydroxybenzoate.

Besides the above preparations, inhalants, eye drops and nose drops may also be formulated in accordance with known methods.

The medicine for treating cancer of this invention is useful for treating various cancer and carcinoma. Examples of such cancer and carcinoma include cancer or carcinoma of brain, nerve and oculus such as pituitary adenoma, acoustic neurilemoma, glioma, brain tumor; cancer and carcinoma of head and neck region such as oral cancer (i.e. tongue cancer, carcinoma of the mouth floor, carcinoma of gingiva, carcinoma of the buccal mucosa, etc.), pharyngeal cancer (i.e. nasopharyngeal cancer, oropharyngeal cancer, hypopharyngeal cancer), laryngeal cancer (i.e. glottic laryngeal cancer, etc.), maxillary cancer, thyroid cancer (i.e. papillary carcinoma, follicular carcinoma, medullary carcinoma, undifferentiated carcinoma, malignant lymphoma, etc.), sialoma (i.e. parotid abscess, cancer of submandibular gland, cancer of sublingual gland, etc.); cancer and carcinoma of breast such as thymoma, breast cancer, lung cancer, mesothelioma; cancer and carcinoma of digestive organ such as stomach cancer, esophageal cancer, colon cancer; cancer and carcinoma of liver, gallbladder and pancreas such as hepatocarcinoma, cholangiocarcinoma, pancreatic cancer, gallbladder cancer, pancreatic endocrine tumors; cancer and carcinoma of uropoietic organ such as penile carcinoma, testicular cancer, renal pelvic and ureter carcinoma, prostate cancer, renal cell carcinoma, bladder carcinoma; cancer and carcinoma of gynecologic such as vulvar cancer, uterine cancer, cervical cancer, corpus uteri carcinoma (endometrial

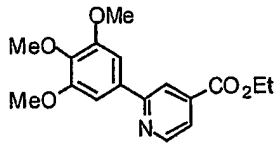
carcinoma), uterine sarcoma, trophoblastic disease, vaginal cancer, mammary carcinoma, ovarian cancer, germ cell tumor of ovary; cancer and carcinoma of cutis such as melanoma, mycosis fungoides, skin cancer; cancer and carcinoma of bone and muscle such as malignant bone tumors (i.e. bone cancer, parosteal osteosarcoma, periosteal osteosarcoma, malignant fibrous histiocytoma, chordoma, diffuse endothelioma of bone, adamantinoma, chondrosarcoma, etc), soft part sarcoma (i.e. malignant fibrous histiocytoma, liposarcoma, synovial sarcoma, leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, perithelioma, lymphagiosarcoma, neurosarcoma, malignant neuroepithelioma, soft part Ewing, extraskeletal chondrosarcoma, extraskeletal osteosarcoma, alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, etc); cancer and carcinoma of blood and lymph such as malignant lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, myelodysplastic syndromes, multiple myeloma, acute myelogenous leukemia, acute lymphocytic leukemia, adult T-cell leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia, chronic myeloproliferative disorders; cancer and carcinoma of endocrine such as melanocytoma, pancreatic endocrine tumors, parathyroid cancer, adrenal tumor; cancer and carcinoma of childhood such as soft part sarcoma, cerebral tumor, retinoblastoma, Wilms' tumor;, and other unidentified cancer.

The dose of the medicine for treating cancer according to the present invention varies according to the age, weight and condition of the patient to be treated, the administration method, the number of times of administration, and the like. It is however preferred that the medicine is generally orally or parenterally administered at once or in several portions in a dose of 1 to 1,000 mg per day in terms of compound (1), for an adult.

The present invention will hereinafter be described in more detail by Examples. However, the present invention is not limited to these examples.

Preparation Example 1

Synthesis of ethyl 2-(3,4,5-trimethoxyphenyl)isonicotinate:



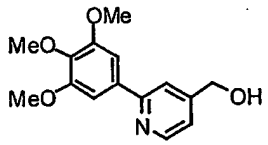
3,4,5-Trimethoxyphenylboronic acid (20.10 g) and ethyl 2-chloroisonicotinate (18.56g) were suspended in a mixted solvent of toluene (200 mL) and THF(100mL), and to the suspension 2 M sodium carbonate (200 mL) and tetrakis(triphenyl phosphine) palladium(0) (5.78 g) were added. The mixture was stirred at 90°C overnight under an argon atmosphere. Ethyl acetate was added to the reaction mixture to separate an organic layer. The organic layer was washed with brine, dried over anhydrous sodium magnesium and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate (5:1) to give the title compound.

Yield: 27.99 g (88%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (t, 3H, J=7.0 Hz), 3.92 (s, 3H), 3.99 (s, 6H), 4.46 (q, 2H, J=7.0 Hz), 7.30 (s, 2H), 7.76 (dd, 1H, J=5.1 Hz, 1.6 Hz), 8.24 (dd, 1H, J=1.6 Hz, 0.8 Hz), 8.81 (dd, 1H, J=5.1 Hz, 0.8 Hz).

Preparation Example 2

Synthesis of 4-hydroxymethyl-2-(3,4,5-trimethoxyphenyl)pyridine:



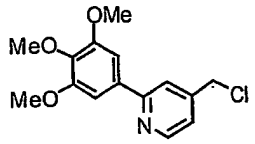
Ethyl 2-(3,4,5-trimethoxyphenyl)isonicotinate (24.57 g) was dissolved in dry THF (200 mL), and to the solution lithium aluminum hydride (2.94 g) was added at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 1 hour as it is. A small amount of water and then sodium sulfate were added to the reaction mixture, and the reaction mixture was filtered through celite. The filtrate was evaporated, and the reultant crude crystals were recrystalized from ethyl acetate-hexane to give the title compound.

Yield: 17.53 g (82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.90 (s, 3H), 3.95 (s, 6H), 4.79 (s, 2H), 7.19 (d, 1H, J=5.1 Hz), 7.21 (s, 2H), 7.66 (s, 1H), 8.60 (d, 1H, J=5.1 Hz).

Preparation Example 3

Synthesis of 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine:



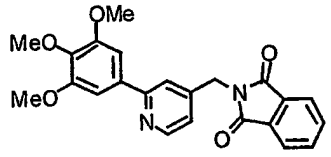
4-hydroxymethyl-2-(3,4,5-trimethoxyphenyl)pyridine(19.18g) was dissolved in chloroform (100 mL), and to the solution thinly chloride (10.2 mL) was added at 0°C. After 30 minutes, the mixture was warmed to room temperature and stirred for 4 hours. The reaction mixture was washed with aqaueous saturated sodium hydrogendcarbonate and brine, dried over anhydrous sodium sulfate and evaporated. The residue was then recrystallized from ethyl acetate-hexane to give the title compound as pale yellow crystalline powder.

Yield: 18.24 g (89%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.91 (s, 3H), 3.97 (s, 6H), 4.61 (s, 2H), 7.24 (s, 2H), 7.26 (d, 1H, J=5.1 Hz), 7.68 (s, 1H), 8.67 (d, 1H, J=5.1 Hz).

Preparation Example 4

Synthesis of N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]phthalimide:

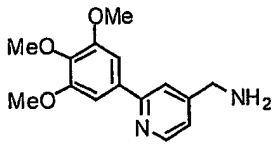


To a solution of 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (881 mg) in chloroform (10 mL) was added potassium phthalimide (556 mg). The mixture was stirred at room temperature overnight and water was added. After separating the organic layer, the aqueous layer was extracted with chloroform. Organic layers were combined, dried over anhydrous magnesium sulfate and evaporated to give the title compound as white powder.

Yield: 1.16 g (96%).

Preparation Example 5

Synthesis of 4-aminomethyl-2-(3,4,5-trimethoxyphenyl)pyridine:

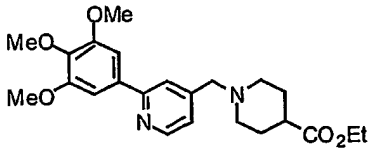


To a suspension of N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] phthalimide (1.16 g) in ethanol (30 mL) was added hydrazine monohydrate (1 mL). The mixture was refluxed for 3 hours. After cooling, the precipitates were filtered off. The filtrate was evaporated and the residue was dissolved in chloroform. The solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous magnesium sulfate and evaporated to give the title compound as pale yellow oil.

Yield: 418 mg (53%).

Preparation Example 6

Synthesis of ethyl 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine-4-carboxylate:



To a solution of ethyl piperidine-4-carboxylate (514 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (969 mg) in acetonitrile (20 mL) was added potassium carbonate (452 mg). The mixture was stirred at room temperature for 4 hours and evaporated. The residual oil was subjected to a column of silica gel and eluted using hexane-ethyl acetate (2:1) and then chloroform-methanol (40:1). Fractions containing the product were collected and evaporated to give the title compound as white prisms .

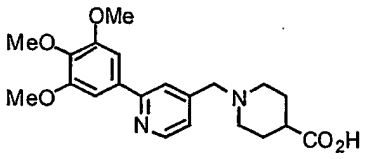
Yield: 1.20 g (88%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25 (t, 3H, J=7.0 Hz), 1.72-1.93 (m, 4H), 2.10 (t, 2H,

J=9.8 Hz), 2.27-2.35 (m, 1H), 2.86 (d, 2H, J=11.3 Hz), 3.55 (s, 2H), 3.91 (s, 3H), 3.98 (s, 6H), 4.14 (q, 2H, J=7.0 Hz), 7.21 (d, 1H, J=4.9 Hz), 7.24 (s, 2H), 7.63 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Preparation Example 7

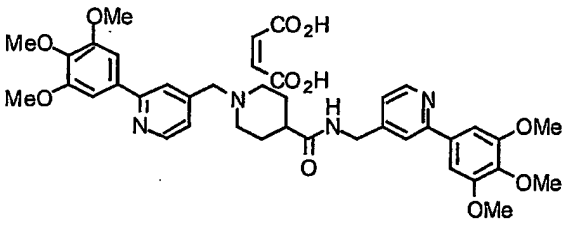
Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine-4-carboxylic acid:



To a solution of ethyl 1-[[2-(3,4,5-trimethoxyphenyl)prydine-4-yl]methyl] piperidine-4-carboxylate (760 mg) in ethanol (10 mL) was added 1 M sodium hydroxide (10 mL). The mixture was stirred at room temperature for 4 hours and evaporated. The residue was dissolved in water (20 mL) and 5% aqueous potassium hydrogen sulfate was added dropwise until pH of the solution became 7. Precipitates were collected and the product was used for the next steps without further purification. Yield: 779 mg (theoretical amount).

Example 1

Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-[[2- (3,4,5-trimethoxyphenyl)pyridin-4-yl]methylaminocarbonyl]piperidine maleate:



To a solution of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] piperidine-4-caroxylic acid (97 mg) and 4-aminomethyl-2-(3,4,5-trimethoxyphenyl) pyridine (68 mg) in acetonitrile (5 mL) was added HBTU (95 mg). The mixture was stirred at room temperature for 12 hours and evaporated. The residual oil was dissolved in chloroform, washed with saturated aqueous sodium hydrogen carbonate

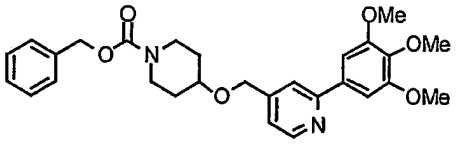
and brine, dried over anhydrous magnesium sulfate and evaporated. Resulting residue was applied to a column of silica gel and eluted using chloroform-methanol (40:1) and then chloroform-methanol (20:1). Fractions containing the product were collected and evaporated. The free base of the product was then converted to a maleate by the usual method.

Yield: 93 mg (49%).

^{1}H-NMR (400 MHz, measured as a maleate, DMSO-d_6) δ: 1.87-2.01 (m, 4H), 2.48-2.56 (m, 1H), 2.78-2.86 (m, 2H), 3.26-3.31 (m, 2H), 3.78 (s, 3H), 3.79 (s, 3H), 3.87 (s, 6H), 3.90 (s, 6H), 4.15 (s, 2H), 4.39 (d, 2H, J=5.9 Hz), 6.16 (s, 2H), 7.16 (d, 1H, J=5.9 Hz), 7.35 (s, 2H), 7.39 (d, 1H, J=5.9 Hz), 7.39 (s, 2H), 7.73 (s, 1H), 7.95 (s, 1H), 8.15 (d, 1H, J=5.9 Hz), 8.54 (d, 1H, J=4.9 Hz), 8.68 (d, 1H, J=4.9 Hz).

Preparation Example 8

Synthesis of 1-(benzyloxycarbonyl)-4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyloxy]piperidine:



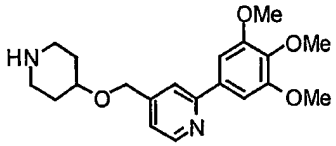
To a solution of 1-(benzyloxycarbonyl)-4-hydroxypiperidine (1.00 g) in DMF (20 mL) was added sodium hydride (55% dispersion in mineral oil, 222 mg). The mixture was stirred at room temperature for 1 hour and then, 4-chlolromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (1.37 g) and potassium iodide (755 mg) was added. The mixture was stirred at 70°C overnight, poured into water and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residual oil was applied to a column of silica gel and column chromatography was performed using chloroform-methanol (99:1) as an eluent giving the title compound.

Yield: 213 mg (10%).

^{1}H NMR (400MHz, $CDCl_3$) δ: 1.63 (br, 2H), 1.89 (br, 2H), 3.20-3.35 (m, 2H), 3.57-3.68 (m, 1H), 3.84-3.92 (m, 5H), 3.94 (s, 6H), 4.62 (s, 2H), 5.11 (s, 2H), 7.21-7.35 (m, 8H), 7.61 (s, 1H), 8.61 (d, 1H, J=5.0Hz).

Preparation Example 9

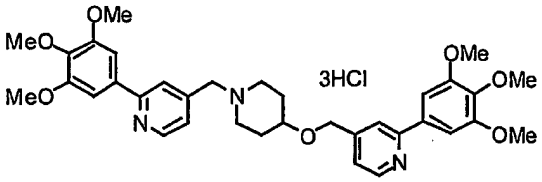
Synthesis of 4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyloxy]piperidine:



To a solution of 1-(benzyloxycarbonyl)-4-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl]methyloxy]piperidine (213 mg) in methanol (10 mL) was added 40% aqueous potassium hydroxide (10 mL). The mixture was stirred at 100°C for 3 hours and evaporated. Water was added to the residue and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residual oil was subjected to column chromatography of silica gel using chloroform-ammonia saturated methanol (20:1) to give the title compound.
Yield: 93 mg (60%).
^{1}H NMR (400MHz, $CDCl_3$) δ: 1.55-1.68 (m, 2H), 2.01 (br, 2H), 2.67-2.72 (m, 2H), 3.13-3.18 (m, 2H), 3.50-3.60 (m, 1H), 3.91 (s, 3H), 3.97 (s, 6H), 4.64 (s, 2H), 7.22 (d, 1H, J=4.3 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.63 (d, 1H, J=5.1 Hz).

Example 2

Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyloxy]piperidine trihydrochloride:



4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyloxy]piperidine (70 mg), 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (22 mg), potassium carbonate (56 mg) and potassium iodide (40 mg) were suspended in acetonitrile (5 mL). The mixture was stirred at room temperature for 5 hr and evaporated. Chloroform and water were added to the residual oil and the organic layer was separated. Aqueous layer was then extracted with chloroform and the organic layers were combined, dried over anhydrous magnesium sulfate and evaporated. The residue was applied to a column of silica gel using chloroform-methanol (40:1) as an eluent. Fractions

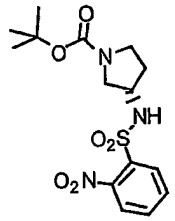
containing the product were collected and evaporated. The title compound was obtained by converting the free base to a trihydrochloride.

Yield: 42 mg (39%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.53-2.42 (m, 6H), 2.80 (br, 2H), 3.57 (br, 3H), 3.88 (s, 6H), 3.94 (s, 6H), 3.95 (s, 6H), 4.60 (s, 2H), 7.18-7.24(m, 6H), 7.61 (s, 2H), 8.58-8.61 (m, 2H).

Preparation Example 10

Synthesis of (3S)-1-(*tert*-butoxycarbonyl)-3-[(2-nitrobenzene)sulfonylamino] pyrrolidine:



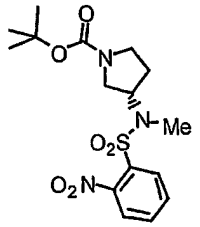
To an ice-cooled solution of(3S)-3-amino-1-(*tert*-butoxycarbonyl) pyrrolidine (404 mg) and triethylamine (220 mg) in THF (5 mL) was added 2-nitrobenzenesulfonyl chloride (481 mg). The mixture was stirred at room temperature for 30 minutes and evaporated. Ethyl acetate was added to the residue. The solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The residual oil was subjected to a column of silica gel and column chromatography was performed using chroloform-methanol (20:1) as an eluent. Fractions containing the product were collected and evaporated to give the title compound as pale yellow amorphous.

Yield: 597 mg (74%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.80-2.12 (m, 2H), 3.14-3.44 (m, 4H), 4.02 (br, 1H), 5.48 (d, 1H, J=7.2 Hz), 7.77 (t, 2H, J=4.4 Hz), 7.87-7.90 (m, 1H), 8.17-8.19 (m, 1H).

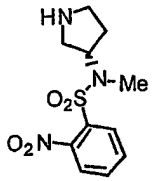
Preparation Example 11

Synthesis of (3S)-1-(*tert*-butoxycarbonyl)-3-[N-methyl-N-(2-nitrobenzene) sulfonylamino]pyrrolidine :



To a suspension of (3S)-1-(*tert*-butoxycarbonyl)-3-[(2-nitrobenzene) sulfonylamino]pyrrolidine (371 mg) and potassium carbonate (141 mg) in acetonitrile (10 mL) was added methyl iodide (141 mg). The mixture was stirred at 60°C for 2 hours and evaporated. Ethyl acetate was added to the mixture. The solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate and evaporated. The residue was applied to a column of silica gel using hexane-ethyl acetate (2:1) as an eluent. Fractions containing the product were collected and evaporated to give the title compound as yellow syrup.
Yield: 365 mg (95%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.95 (br, 1H), 2.09 (br, 1H), 2.87 (s, 3H), 3.20-3.31 (m, 2H), 3.53 (br, 2H), 4.58 (br, 1H), 7.65 (br, 1H), 7.71 (br, 2H), 8.04 (br, 1H).

Preparation Example 12
Synthesis of (3S)-3-[N-methyl-N-(2-nitrobenzene)sulfonylamino]pyrrolidine :

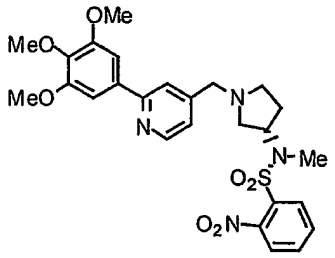


To an ice-cooled solution of (3S)-1-(*tert*-butoxycarbonyl)-3-[N-methyl-N-(2-nitrobenzenesulfonyl)amino]pyrrolidine (365 mg) in dichloromethane (25 mL) was added trifluoroacetic acid (1 mL). The mixture was stirred at room temperature for 3 hours and evaporated. The residue was dissolved in chloroform. The solution was washed with saturated aqueous sodium hydrogen carbonate and brine, dried over anhydrous sodium sulfate and evaporated to give the title compound as yellow syrup.
Yield: 135 mg (50%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.69-1.74 (m, 1H), 1.87 (br, 1H), 1.95-2.02 (m, 1H), 2.80 (dd, 1H, J=11.7 Hz, 5.7 Hz), 2.84-2.91 (m, 4H), 2.96-3.05 (m, 1H), 3.10 (dd, 1H,

J=11.7 Hz, 8.2 Hz), 4.48-4.56 (m, 1H), 7.61-7.63 (m, 1H), 7.66-7.73 (m, 2H), 8.01-8.04 (m, 1H).

Preparation Example 13

Synthesis of (3S)-3-[N-methyl-N-(2-nitrobenzene)sulfonylamino]-1- [[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]pyrrolidine :



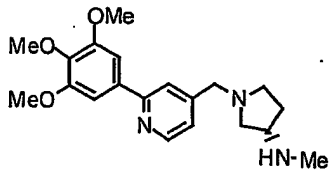
(3S)-3-[N-methyl-N-(2-nitrobenzene)sulfonylamino]pyrrolidine (135 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (139 mg) were coupled in the same manner as described in Example 2 to give the title compound as yellow amorphous .

Yield: 247 mg (96%).

^{1}H-NMR (400 MHz, CDCl3) δ: 1.80-1.87 (m, 1H), 2.15-2.30 (m, 2H), 2.52 (dd, 1H, J=10.5 Hz, 8.2 Hz), 2.71 (dd, 1H, J=10.5 Hz, 8.2 Hz), 2.90 (dt, 1H, J=8.8 Hz, 2.9 Hz), 2.96 (s, 3H), 3.53 (d, 1H, J=13.9 Hz), 3.68 (d, 1H, J=13.9 Hz), 3.90 (s, 3H), 3.96 (s, 6H), 4.61-4.68 (m, 1H), 7.16 (dd, 1H, J=4.9 Hz, 1.2 Hz), 7.21 (s, 2H), 7.58-7.60 (m, 2H), 7.64-7.69 (m, 2H), 7.99-8.02 (m, 1H), 8.58 (d, 1H, J=4.9 Hz,).

Preparation Example 14

Synthesis of (3S)-3-methylamino-1-[[2-(3,4,5-trimethoxyphenyl)-pyridin-4-yl]methyl]pyrrolidine:



To a solution of (3S)-3-[N-methyl-N-(2-nitrobenzene)sulfonylamino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]pyrrolidine (242 mg) in acetonitrile (5 mL) was added potassium carbonate (94 mg) and thiophenol (75 mg). The mixture

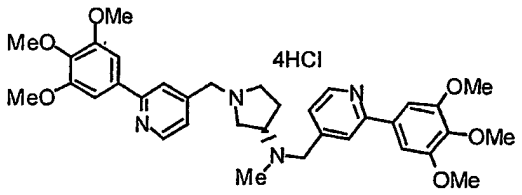
was stirred at 80°C for 3 hours and evaporated. Ethyl acetate was added to the mixture, the solution was washed with saturated aqueous sodium hydrogen carbonate, water, and brine, dried over anhydrous sodium sulfate and evaporated. The residual oil was subjected to preparative TLC using chloroform-methanol (20:1) as a solvent system giving yellow syrup of the title compound.

Yield: 104 mg (64%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (br, 1H), 1.56-1.64 (m, 1H), 2.11-2.17 (m, 1H), 2.38 (s, 3H), 2.44 (dd, 1H, J=7.4 Hz, 4.5 Hz), 2.50-2.55 (m, 1H), 2.66-2.75 (m, 2H), 3.20-3.26 (m, 1H), 3.66 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 7.21 (d, 1H, J=4.1 Hz), 7.25 (s, 2H), 7.64 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).

Example 3

Synthesis of (3S)-3-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]pyrrolidine tertrahydrochloride.



(3S)-3-methylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] pyrrolidine (104 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (85 mg) was condensed in the same manner as described in Example 2. Yellow syrup obtained was converted to a tetrahydrochloride by the usual method giving the title compound as yellow powder.

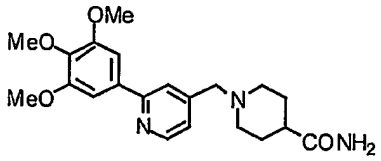
Yield: 151 mg (68%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.89-1.92 (m, 1H), 2.04-2.08 (m, 1H), 2.18 (s, 3H), 2.60-2.76 (m, 4H), 3.25-3.29 (m, 1H), 3.53 (d, 1H, J=14.3 Hz), 3.62 (d, 1H, J=14.3 Hz), 3.64 (d, 1H, J=13.9 Hz), 3.73 (d, 1H, J=13.9 Hz), 3.89 (s, 6H), 3.95 (s, 6H), 3.96 (s, 6H), 7.20-7.21 (m, 2H), 7.23 (s, 2H), 7.24 (s, 2H), 7.61 (s, 1H), 7.65 (s, 1H), 8.59 (d, 1H, J=5.7 Hz), 8.60 (d, 1H, J=5.3 Hz).

Preparation Example 15

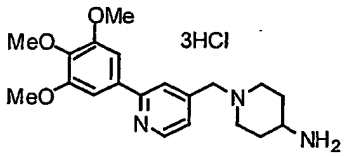
Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine-4-

carboxamide:



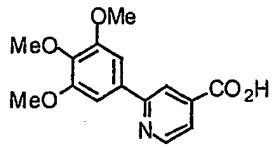
Piperidine-4-carboxamide (385 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (881 mg) were condensed by the same method as described in Example 2 to give the title compound as white needles .
Yield: 1.01 g (87%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.70-1.88 (m, 4H), 2.01-2.23 (m, 3H), 2.95 (d, 2H, J=11.0 Hz), 3.56 (s, 2H), 3.90 (s, 3H), 3.98 (s, 6H), 5.46 (d, 2H, J=16.3 Hz), 7.21 (d, 1H, J=5.0 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.59 (d, 1H, J=5.0 Hz).

Preparation Example 16
Synthesis of 4-amino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



To a solution of 1-[[2-(3,4,5-trimethoxypheyl)pyridin-4-yl]methyl]piperidine-4-carboxamide (192 mg) in a mixed solvent of water (50 mL) and acetonitrile (50 mL) was added [bis(trifluoroacetoxy)iodo]benzene (323 mg). The mixture was stirred at room temperature overnight and evaporated. Saturated aqueous sodium hydrogen carbonate was added to the residue and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated. Yellow syrup obtained was then converted to trihydrochloride which gave yellow powder. The title compound was used for next step without further purification.
Yield: 201 mg (theoretical amount).

Preparation Example 17
Synthesis of 2-(3,4,5-trimethoxyphenyl)isonicotinic acid:

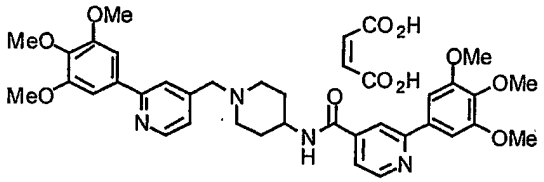


To a solution of ethyl 2-(3,4,5-trimethoxyphenyl)isonicotinate (3.17 g) in ethanol (40 mL) was added 10% potassium hydroxide (2.42 g). The mixture was stirred at room temperature for 5 hours and evaporated. Water was added to the residue and pH was adjusted to 7. White precipitates of the title compound were collected by filtration and the compound was used for next step without further purification.

Yield: 2.60 g (90%).

Example 4

Synthiesis of 4-[2-(3,4,5-trimethoxyphenyl)pyridin-4-carbonylamino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine maleate:



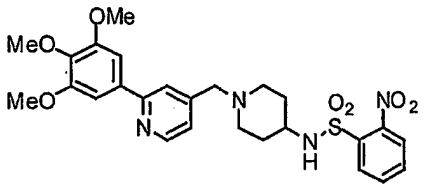
2-(3,4,5-trimethoxyphenyl)isonicotinic acid (72 mg) and 4-amino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (117 mg) were condensed in the same manner as described in Example 1. The title compound was obtained as a maleate.

Yield: 173 mg (93%).

^{1}H-NMR (400 MHz, measured as a maleate, DMSO-d_6) δ: 1.82-1.94 (m, 2H), 2.03-2.08 (m, 2H), 2.77-2.83 (m, 2H), 3.20-3.27 (m, 2H), 3.79 (s, 6H), 3.90 (s, 12H), 4.00 (br, 1H), 4.06 (s, 2H), 6.15 (s, 2H), 7.36-7.38 (m, 1H), 7.39 (s, 2H), 7.41 (s, 2H), 7.61-7.63 (m, 1H), 7.90 (s, 1H), 8.12 (s, 1H), 8.27-8.32 (m, 1H), 8.67 (d, 1H, J=4.9 Hz), 8.74 (d, 1H, J=5.1 Hz).

Preparation Example 18

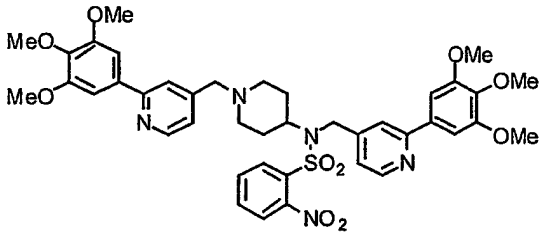
Synthesis of 4-[(2-nitrobenzene)sulfonylamino]-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl]methyl]piperidine:



4-amino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (467 mg) and 2-nitrobenzenesulfonyl chloride (244 mg) were condensed in the same manner as described in Preparation Example 10 to give the title compound.
Yield: 494 mg (91%).

Preparation Example 19

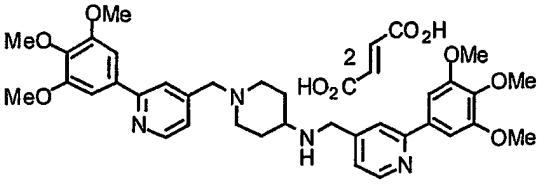
Synthesis of 4-[N-(2-nitrobenzene)sulfonyl-N-[[2-(3,4,5-trimethoxyphenyl)–pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphneyl)pyridin-4-yl]methyl]piperidine:



4-[(2-nitrobenzene)sulfonylamino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (494 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (267 mg) were condensed in the same manner as described in Example 2 to give the title compound.
Yield: 443 mg (61%).

Example 5

Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methylamino]piperidine difumalate:



4-[N-(2-nitrobenzene)sulfonyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]amino]-1-[[2-(3,4,5-trimethoxyphneyl)pyridin-4-yl]methyl]piperidine (443 mg) was treated in the same manner as described in Preparation Example 14. The title

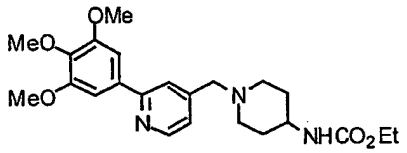
compound was obtained after converting to a difumalate.

Yiled: 103 mg (24%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ: 1.44-1.53 (m, 2H), 1.87-1.91 (m, 2H), 2.15 (t, 2H, J=1.1 Hz), 2.57-2.64 (m, 1H), 2.82-2.85 (m, 2H), 3.59 (s, 2H), 3.78 (s, 6H), 3.89 (s, 12H), 3.90 (s, 2H), 6.63 (s, 4H), 7.24 (d, 1H, J=4.9 Hz), 7.29 (d, 1H, J=4.9 Hz), 7.35 (s, 2H), 7.37 (s, 2H), 7.76 (s, 1H), 7.85 (s, 1H), 8.53-8.56 (m, 2H).

Preparation Example 20

Synthesis of 4-(ethoxycarbonylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



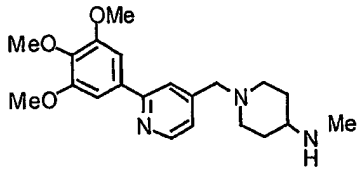
To a solution of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] piperidine-4-carboxamide (528 mg) in a mixed solvent of ethanol (10 mL) and acetonitrile (10 mL) was added [bis(trifluoroacetoxy)iodo]benzene (884 mg). The mixture was stirred at room temperature overnight and evaporated. Saturated aqueous sodium hydrogen carbonate was added to the residue and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was applied to a column of silica gel and purified using chloroform-methanol (20:1) as an eluent to give the title compound.

Yield: 566 mg (96%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, 3H, J=7.0 Hz), 1.40-1.51 (m, 2H), 1.92 (d, 2H, J=10.9 Hz), 2.15 (t, 2H, J=10.9 Hz), 2.78 (d, 2H, J=11.6 Hz), 3.52 (br, 3H), 3.87 (s, 3H), 3.94 (s, 6H), 4.07 (q, 2H, J=7.0 Hz), 4.56 (br, 1H), 7.17 (d, 1H, J=4.9 Hz), 7.21 (s, 2H), 7.59 (s, 1H), 8.56 (d, 1H, J=5.1 Hz).

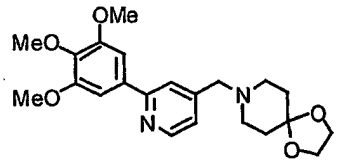
Preparation Example 21

Synthesis of 4-(methylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] piperidine:



To a suspension of lithium aluminum hydride (100 mg) in dry THF (50 mL) was added a solution of 4-(ethoxycarbonylamino)-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl]methyl]piperidine (566 mg) in dry THF (50 mL) under an argon atmosphere. The mixture was then refluxed overnight, then cooled down. Saturated aqueous ammonium chloride was added to the mixture and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to silica gel column chromatography using chloroform-ammonia saturated methanol (9:1) to give the title compound as yellow oil.
Yiled: 379 mg (78%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36-1.46 (m, 2H), 1.89 (d, 2H, J=12.5 Hz), 2.10 (dt, 2H, J=11.5 Hz, 1.1 Hz), 2.35-2.43 (m, 1H), 2.43 (s, 3H), 2.86 (d, 2H, J=11.6 Hz), 3.56 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 7.21 (d, 1H, J=5.1 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.59(d, 1H, J=4.9 Hz).

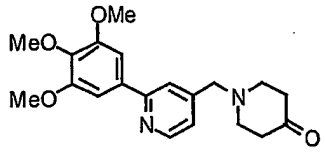
Preparation Example 22
Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone ethylene ketal:



4-Piperidone ethylene ketal (12.0 g) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (12.3 g) was condensed in the same manner as described in Example 2 to give the title compound.
Yield: 19.0 g (theoretical amount).
^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.68 (t, 4H, J=5.6 Hz), 2.48 (br, 4H), 3.50 (s, 2H), 3.82 (s, 3H), 3.86 (s, 4H), 3.88 (s, 6H), 7.13 (d, 1H, J=4.9 Hz), 7.17 (s, 2H), 7.57 (s, 1H), 8.51 (d, 1H, J=4.9 Hz).

Preparation Example 23

Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone:



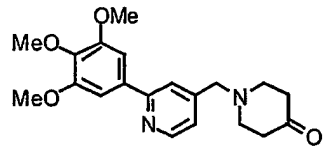
To a solution of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]- 4-piperidone ethylene ketal (19.0 g) in THF (200 mL) was added 1 M hydrochloric acid (200 mL). The mixture was stirred at 90°C overnight, then neutralized with 2 M sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residual oil was applied to a column of silica gel using chloroform-methanol (40:1) as an eluent. Fractions containing the product were collected and evaporated to give the title compound.

Yield: 15.0 g (75%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 2.48 (t, 4H, J=6.1 Hz), 2.79 (t, 4H, J=6.0 Hz), 3.69 (s, 2H), 3.89 (s, 3H), 3.96 (s, 6H), 7.24 (s, 2H), 7.26 (d, 1H, J=4.9 Hz), 7.66 (s, 1H), 8.62 (d, 1H, J=4.9 Hz).

Preparation Example 24

Synthesis of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone:



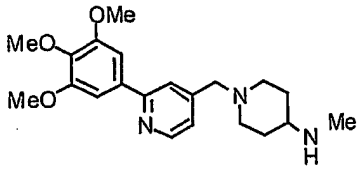
4-Piperidone hydrochloride monohydrate (3.07 g) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (2.94 g) were coupled by the same manner as described in Example 2 to give the title compound.

Yield: 3.55 g (99%).

Preparation Example 25

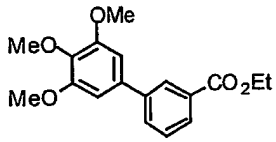
Synthesis of

4-(methylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



To a solution of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (1.00 g) in 1,2-dichloroethane (60 mL) was added 30% solution of methylamine in ethanol (750 mg) and sodium triacetoxyborohydride (1.66 g). The mixture was stirred at room temperature for 3 hours, then small amount of water was added and evaporated. Water was added to the residue and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to silica gel column chromatography using chloroform-methanol (40:1) to give the title compound.
Yield: 640 mg (62%).

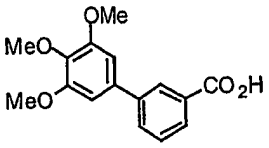
Preparation Example 26
Synthesis of ethyl 3-(3,4,5-trimethoxyphenyl)benzoate:



3,4,5-Trimethoyphenylboronic acid (3.7 g) and ethyl 3-bromobenzoate (4.02 g) were condensed in the same manner as described in Preparation Example 1 to give the title compound.

Yield: 5.09 g (92%).
^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.42 (t, 3H, J=7.1 Hz), 3.90 (s, 3H), 3.94 (s, 6H), 4.41 (q, 2H, J=7.1 Hz), 6.79 (s, 2H), 7.50 (t, 1H, J=7.8 Hz), 7.73 (dt, 1H, J=7.1 Hz, 1.5 Hz), 8.01 (dt, 1H, J=7.8 Hz, 1.4 Hz), 8.23 (t, 1H, J=1.8 Hz).

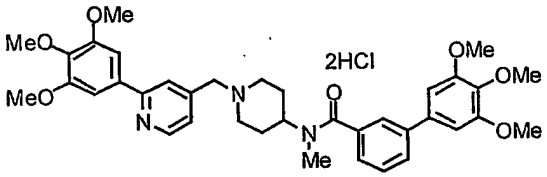
Preparation Example 27
Synthesis of 3-(3,4,5-trimethoxyphenyl)benzoic acid:



Ethyl 3-(3,4,5-trimethoxyphenyl)benzoate (1.19 g) was treated in the same manner as described in Preparation Example 17 to give the title compound.
Yield: 986 mg (91%).

Example 6

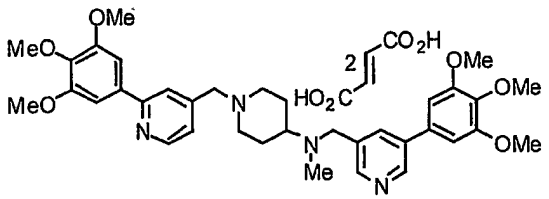
Synthesis of 4- [N-methyl-N-[3-(3,4,5-trimethoxyphenyl)]benzoylamino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



3-(3,4,5-trimethoxyphenyl)benzoic acid (1.03 g) and 4-(methylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (1.32 g) were condensed in the same method as described in Example 1. The title compound was obtained after converting a free amine to a dihydrochloride.
Yield: 1.44 g (57%).
^{1}H-NMR (400 MHz, measured as a dihydrochloride, DMSO-d_6) δ : 1.89 (d, 2H, J=11.7 Hz), 2.54-2.62 (m, 2H), 2.89 (s, 3H), 3.09 (t, 2H, J=12.7 Hz), 3.43 (d, 2H, J=14.4 Hz), 3.76 (s, 3H), 3.78 (s, 3H), 3.88 (s, 6H), 3.91 (s, 6H), 4.34 (br, 3H), 6.91 (s, 2H), 7.33 (d, 1H, J=7.6 Hz), 7.47-7.51 (m, 2H), 7.54 (s, 2H), 7.60 (s, 1H), 7.71 (d, 1H, J=7.8 Hz), 8.55 (s, 1H), 8.68 (d, 1H, J=5.1 Hz).

Example 7

Synthesis of 4-[N-methyl-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine difumarate:



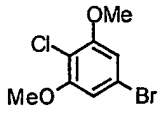
4-methylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (135 mg) and 3-chloromethyl-5-(3,4,5-trimethoxypyenyl)pyridine (107 mg) were condensed by the same method as described in Example 2. White powder of the title compound was obtained after converting a free base to a difumarate.

Yield: 180 mg (58%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ: 1.69-1.73 (m, 2H), 1.82-1.85 (m, 2H), 2.03-2.08 (m, 2H), 2.25 (s, 3H), 2.48-2.51 (m, 1H), 2.97-2.99 (m, 2H), 3.56 (s, 2H), 3.67 (s, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 3.94 (s, 6H), 3.98 (s, 6H), 6.76 (s, 2H), 7.22 (d, 1H, J=5.1 Hz), 7.24 (s, 2H), 7.62 (s, 1H), 7.80 (s, 1H), 8.50 (d, 1H, J=2.0 Hz), 8.60 (d, 1H, J=4.3 Hz), 8.69 (d, 1H, J=5.1 Hz).

Preparation Example 28

Synthesis of 1-bromo-4-chloro-3,5-dimethoxybenzene:

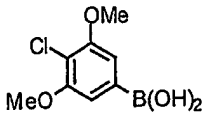


A solution of sodium nitrite (97 mg) in water (2.0 mL) was added dropwise to an ice-cold suspension of 4-bromo-2,6-dimethoxyaniline (232 mg) in 6.0 M hydrochloric acid (2.5 mL). After stirring in ice for 30 minutes, a solution of cupric chloride (495 mg) in concentrated hydrochloric acid (2.0 mL) was added. The reaction mixture was stirred at room temperature for 30 minutes, then at 100°C for 2 hours, and extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium hydrogencarbonate and water, dried over anhydrous sodium sulfate, and evaporated. The residue was subjected to a column of silica gel using hexane-ethyl acetate (10:1) as an eluent to give the title compound as white powder.

Yield: 230 mg (92%).

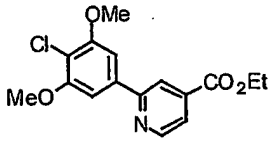
Preparation Example 29

Synthesis of 4-chloro-3,5-dimethoxyphenylboronic acid:



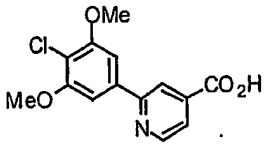
Under an argon atomsphere, to dry THF (2 mL) stirred in a dry ice-methanol bath was gradually added a 1.57 M solution of n-butyllithium in hexane (0.8 mL), followed by the dropwise addition of a solution of 1-bromo-4-chloro-3,5-dimethoxybenzene (160 mg) in dry THF (2 mL). After the mixture was stirred for 20 minutes in the dry ice-methanol bath, triisopropyl borate (0.18 mL) was added and the mixture was additionally stirred for 20 minutes. The reaction mixture was then stirred at room temperature for 1 hour and pH of the mixture was adjusted at 3 using 4 M hydrochloric acid. The mixture was stirred at 0°C for 1 hour and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was recrystallized from ethyl acetate-hexane giving the title compound as white powder.
Yield: 90 mg (66%).

Preparation Example 30
Synthesis of ethyl 2-(4-chloro-3,5-dimethoxyphenyl)isonicotinate:



4-Chloro-3,5-dimethoxyphenylboronic acid (7.45 g) and ethyl 2-chloroisonicotinate (6.39 g) were condensedn in the same manner as described in Preparation Example 1 to give the title compound.
Yield: 8.55 g (77%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (t, 3H, J=7.3 Hz), 4.03 (s, 6H), 4.45 (q, 2H, J=7.3 Hz), 7.32 (s, 2H), 7.80 (d, 1H, J=5.1 Hz), 8.27 (s, 1H), 8.83 (d, 1H, J=5.0 Hz).

Preparation Example 31
Synthesis of 2-(4-chloro-3,5-dimethoxyphenyl)isonicotinic acid:



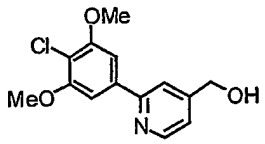
To a solution of ethyl 2-(4-chloro-3,5-dimethoxyphenyl)isonicotinate (8.55 g) in ethanol (80 mL) was added 2 M sodium hydroxide (100 mL). The mixture was refluxed for 30 min and evaporated. The aqueous layer was neutralized by 1 M hydrochloric acid and precipitates were dissolved in a mixed solvent of ethyl acetate-THF (3:1). After drying over anhydrous sodium sulfate, the solvent was evaporated to give the title compound.

Yield: 7.20 g (92%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.02 (s, 6H), 7.34 (s, 2H), 7.83 (d, 1H, J=4.9 Hz), 7.84 (s, 1H), 8.82 (d, 1H, J=4.9 Hz).

Preparation Example 32

Synthesis of 2-(4-chloro-3,5-dimethoxyphenyl)-4-hydroxymethylpyridine:



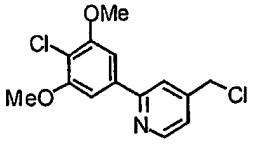
To an ice-cooled solution of 2-(4-chloro-3,5-dimethoxyphenyl)isonicotinic acid (7.20 g) and triethylamine (5.6 mL) in THF (70 mL) was added ethyl chloroformate (2.8 mL). The mixture was stirred at room temperature for 1 hour and filtered. To the filtrate was then added a solution of sodium borohydride (1.25 g) in water (4 mL). The mixture was stirred at room temperature for another hour and evaporated. Water was added to the residue and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to silica gel column chromatography using chloroform-methanol (20:1) and then chloroform-methanol (15:1) to give the title compound.

Yield: 4.10 g (60%).

^{1}H-NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ: 4.01 (s, 6H), 4.76 (s, 2H), 7.20-7.35 (m, 3H), 7.78 (s, 1H), 8.62 (s,1H).

Preparation Example 33

Synthesis of 2-(4-chloro-3,5-dimethoxyphenyl)-4-chloromethylpyridine:



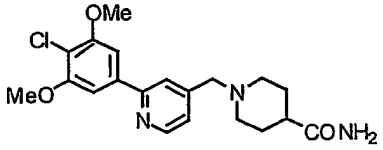
2-(4-Chloro-3,5-dimethoxyphenyl)-4-hydroxymethylpyridine (4.10 g) was treated in the same manner as described in Preparation Example 3 to give the title compound.

Yield: 4.20 g (96%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.02 (s, 6H), 4.63 (s, 2H), 7.26 (s, 2H), 7.29 (d, 1H, J=4.9 Hz), 7.72 (s, 1H), 8.69 (d, 1H, J=4.9 Hz).

Preparation Example 34

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine-4-carboxamide:



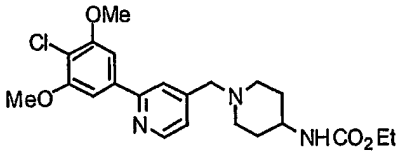
Piperidine-4-carboxamide (301 mg) and 2-(4-chloro-3,5-dimethoxyphenyl)-4-chloromethylpyridine (600 mg) were coupled in the same manner as described in Example 2 to give the title compound.

Yield: 743 mg (95%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.75-1.90 (m, 4H), 2.07-2.25 (m, 3H), 2.94 (d, 2H, J=11.6 Hz), 3.57 (s, 2H), 4.02(s, 6H), 7.24-7.31 (m, 3H), 7.67 (s, 1H), 8.61 (d, 1H, J=5.1 Hz).

Preparation Example 35

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-(ethoxycarbonylamino)piperidine:



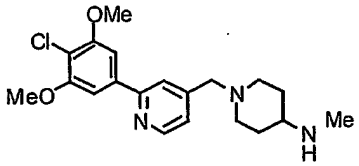
1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine-4-carboxamide (743 mg) was treated in the same manner as described in Preparation Example 20 to give the title compound.

Yield: 887 mg (theoretical amount).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, 3H, J=7.1 Hz), 1.43-1.59 (m, 2H), 1.96 (d, 2H, J=11.4 Hz), 2.19 (t, 2H, J=11.0 Hz), 2.82 (d, 2H, J=11.5 Hz), 3.56 (s, 2H), 4.02 (s, 6H), 4.10 (q, 2H, J=7.1 Hz), 7.26 (s, 2H), 7.66 (s, 1H), 7.71 (dd, 1H, J=5.6 Hz, 1.0 Hz), 8.6 (dd, 1H, J=4.9 Hz, 0.5 Hz).

Preparation Example 36

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-methylaminopiperidine:



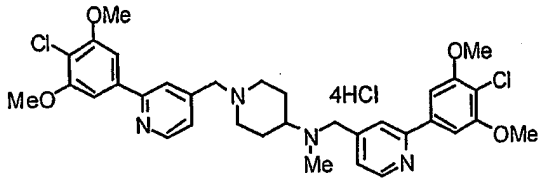
1-[[2-(4-chloro-3,5-diemthoxyphenyl)pyridin-4-yl]methyl]-4-(ethoxy-carbonylamino)piperidine (887 mg) was treated in the same manner as described in Preparation Example 21 to give the title compound.

Yield: 195 mg (27%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35-1.49 (m, 2H), 1.89 (d, 2H, J=12.3 Hz), 2.11 (t, 2H, J=9.4 Hz), 2.38-2.45 (m, 1H), 2.44 (s, 3H), 2.87 (d, 2H, J=10.7 Hz), 3.57 (s, 2H), 4.02 (s, 6H), 7.23-7.29 (m, 3H), 7.68 (s, 1H), 8.61 (d, 1H, J=4.9 Hz).

Example 8

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-[N-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-N-methylamino]piperidine tetrahydrochloride:



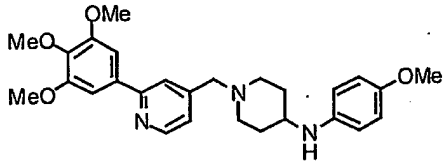
1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-methylamino-piperidine (195 mg) and 2-(4-chloro-3,5-dimethoxyphenyl)-4-chloromethylpyridine (152 mg) were condensed in the same manner as described in Example 2. A free base obtained was converted to a tetrahydrochloride giving yellow powder.

Yield: 300 mg (75%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.60-1.90 (m, 4H), 2.06 (t, 2H, J=11.7 Hz), 2.26 (s, 3H), 2.45-2.55 (m, 1H), 2.97 (d, 2H, J=11.3 Hz), 3.57 (s, 2H), 3.67 (s, 2H), 4.01 (s, 6H), 4.02 (s, 6H), 7.24-7.28 (m, 6H), 7.65 (s, 1H), 7.67 (s, 1H), 8.61 (d, 1H, J=5.4 Hz), 8.62 (d, 1H, J=5.4 Hz).

Preparation Example 37

Synthesis of 4-(*p*-anisidino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-piperidine:



To a solution of 1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (2.17 g) in toluene (40 mL) was added *p*-anisidine (900 mg) and molecular sieves 4A (6.0 g). The mixture was refluxed overnight, then filtered and the filtrate was evaporated. The residual oil was dissolved in ethanol (40 mL) and sodium borohydride (276 mg) was added. The mixture was stirred at room temperature for 2 hours before concentration in vacuo. The residue was dissolved in ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and evaporated. The residual oil was subjected to silica gel column chromatography using chloroform-methanol (50:1) to give the title compound as yellow amorphous.

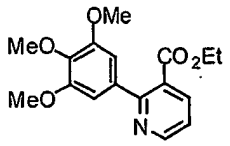
Yield: 1.56 g (55%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.48 (br, 2H), 2.05 (br, 2H), 2.20 (br, 2H), 2.86 (br, 2H), 3.23 (s, 1H), 3.58 (s, 2H), 3.74 (s, 3H), 3.91 (s, 3H), 3.97 (s, 6H), 6.58 (d, 2H, J=8.8

Hz), 6.77 (d, 2H, J=9.0 Hz), 7.22 (d, 1H, J=5.1 Hz), 7.26 (s, 2H), 7.64 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 38

Synthesis of ethyl 2-(3,4,5-trimethoxyphenyl)nicotinate:



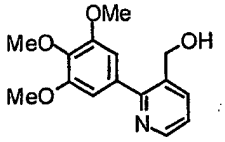
3,4,5-Trimethoxyphenylboronic acid (694 mg) and ethyl 2-chloronicotinate (608 mg) were reacted in the same manner as described in Preparation Example 1 to give the title compound.

Yield: 799 mg (77%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.10 (t, 3H, J=7.2 Hz), 3.89 (s, 9H), 4.19 (q, 2H, J=7.2 Hz), 6.79 (s, 2H), 7.34 (dd, 1H, J=7.8 Hz, 4.8 Hz), 8.06 (dd, 1H, J=7.8 Hz, 1.7 Hz), 8.75 (dd, 1H, J=4.8 Hz, 1.7 Hz).

Preparation Example 39

Synthesis of 3-hydroxymethyl-2-(3,4,5-trimethoxyphenyl)pyridine:



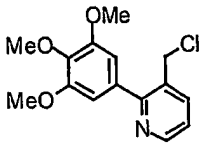
Ethyl 2-(3,4,5-trimethoxyphenyl)nicotinate (468 mg) was treated in the same manner as described in Preparation Example 2 to give the title compound.

Yield: 293 mg (72%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.90 (s, 9H), 4.72 (s, 2H), 6.83 (s, 2H), 7.32 (dd, 1H, J=7.9 Hz, 4.8 Hz), 7.92 (dd, 1H, J=7.9 Hz, 1.7 Hz), 8.62 (dd, 1H, J=4.8 Hz, 1.7 Hz).

Preparation Example 40

Synthesis of 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine:

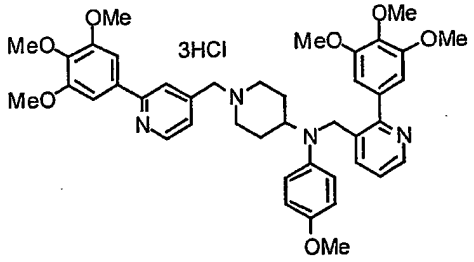


3-Hydroxymethyl-2-(3,4,5-trimethoxyphenyl)pyridine (293 mg) was treated in the same manner as described in the Preparation Example 3 to give the title compound.

Yield: 311 mg (theoretical amount).

Example 9

Synthesis of 4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



To a solution of 4-(*p*-anisidino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]piperidine (139 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) in acetonitrile (5 ml) was added potassium carbonate (83 mg) and potassium iodide (63 mg). The mixture was stirred at 70°C overnight and evaporated. The residue was dissolved in chloroform, washed with water and brine, dried over anhydrous magnesium sulfate and evaporated. The residual oil was applied to a column of silica gel using diethylether-metanol (20:1) as an eluent. A free base obtained was converted to a trihydrochloride to give the title compound as yellow powder.

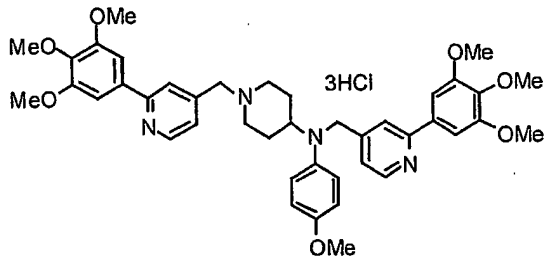
Yield: 16 mg, (8%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.60 (br, 2H), 1.77 (br, 2H), 2.09 (br, 2H), 2.93 (br, 2H), 3.45 (br, 1H), 3.54 (s, 2H), 3.73 (s, 3H), 3.90 (s, 6H), 3.91 (s, 6H), 3.96 (s, 6H), 4.34 (s, 2H), 6.65 (d, 2H, J=9.0 Hz), 6.71 (s, 2H), 6.74 (d, 2H, J=9.0 Hz), 7.16-7.19 (m, 2H), 7.22 (s, 2H), 7.55 (s, 1H), 7.79 (d, 1H, J=7.0 Hz), 8.50

(br, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 10

Synthesis of 4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxypheny)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



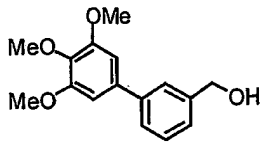
4-(*p*-Anisidino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (1.56g) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (1.08g) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder.

Yield: 1.17 g (40%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.68-1.97 (m, 4H), 2.09-2.23 (m, 2H), 2.98 (br, 2H), 3.54-3.66 (m, 3H), 3.73 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.45 (s, 2H), 6.74 (d, 2H, J=9.2 Hz), 6.79 (d, 2H, J=9.2 Hz), 7.15 (s, 2H), 7.16-7.21 (m, 2H), 7.23 (s, 2H), 7.57 (s, 1H), 7.60 (s, 1H), 8.54 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 41

Synthesis of 3-(3,4,5-trimethoxyphenyl)benzyl alcohol:



Ethyl 3-(3,4,5-trimethoxyphenyl)benzoate (5.09 g) was treated in the same manner as described in Preparation Example 2 to give the title compound.

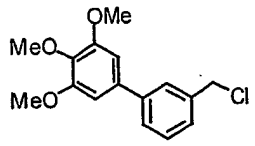
Yield: 4.25 g (97%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.87 (t, 1H, J=6.0 Hz), 3.89 (s, 3H), 3.92 (s, 6H), 4.76

(d, 1H, J=5.6 Hz), 6.77 (s, 2H), 7.34 (d, 1H, J=7.4 Hz), 7.42 (t, 1H, J=7.5 Hz), 7.48 (d, 1H, J=7.6 Hz), 7.55 (s, 1H).

Preparation Example 42

Synthesis of 3-(3,4,5-trimethoxyphenyl)benzyl chloride:



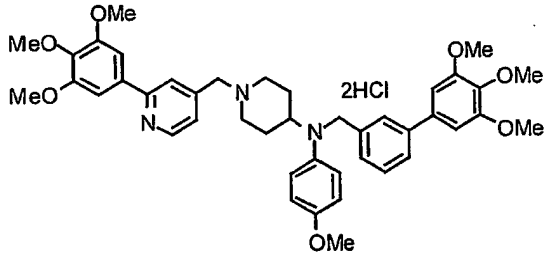
3-(3,4,5-Trimethoxyphenyl)benzyl alcohol (1.21 g) was treated in the same manner as described in Preparation Example 3 to give the title compound.

Yield: 893 mg (69%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.87 (s, 3H), 3.90 (s, 6H), 4.62 (s, 2H), 6.75 (s, 2H), 7.33 (d, 1H, J=7.6 Hz), 7.39 (t, 1H, J=7.7 Hz), 7.48 (d, 1H, J=7.6 Hz), 7.54 (s, 1H).

Example 11

Synthesis of 4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1 -[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



4-(*p*-Anisidino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (139 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a dihydrochloride which gave the title compound as yellow powder.

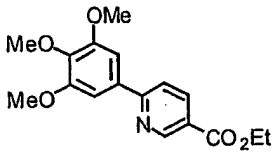
Yield: 52 mg (22%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.77-1.92 (m, 5H), 2.14-2.20 (m, 2H), 2.95-3.00 (m, 2H), 3.58 (s, 2H), 3.72 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.47 (s, 2H), 6.70 (s, 2H), 6.74-6.83 (m, 4H), 7.20 (d, 1H, J=7.4 Hz), 7.23 (s, 2H), 7.25-7.27 (m, 1H), 7.33 (t, 1H, J=7.4 Hz), 7.38 (d, 1H, J=8.7 Hz),

7.43 (s, 1H), 7.62 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Preparation Example 43

Synthesis of ethyl 6-(3,4,5-trimethoxyphenyl)nicotinate:



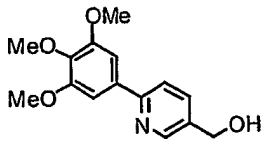
3,4,5-Trimethoxyphneylboronic acid (1.16 g) and ethyl 6-chloronitotinate (1.02 g) were coupled in the same manner as described in the Preparation Example 1 to give the title compound.

Yield: 1.42 g (82%)

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.43 (t, 3H, J=7.2 Hz), 3.92 (s, 3H), 3.98 (s, 6H), 4.44 (q, 2H, J=7.2 Hz), 7.32 (s, 2H), 7.76 (d, 1H, J=8.3 Hz), 8.33 (dd, 1H, J=8.2 Hz, 2.2 Hz), 9.26 (d, 1H, J=2.2 Hz).

Preparation Example 44

Synthesis of 5-hydroxymethyl-2-(3,4,5-trimethoxyphenyl)pyridine:



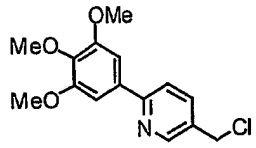
Ethyl 6-(3,4,5-trimethoxyphenyl)nicotinate (658 mg) was treated in the same manner as described in Preparation Example 2 to give the title compound.

Yield: 482 mg (85%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.91 (s, 3H), 3.97 (s, 6H), 4.76 (s, 2H), 7.23 (s, 2H), 7.68 (d, 1H, J=7.4 Hz), 7.78 (dd, 1H, J=7.4 Hz, 2.3 Hz), 8.63 (d, 1H, J=2.3 Hz).

Preparation Example 45

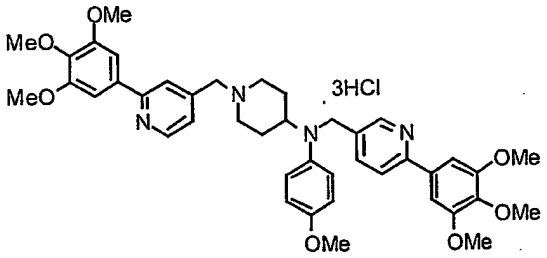
Synthesis of 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine:



5-Hydroxymethyl-2-(3,4,5-trimethoxyphenyl)pyridine (685 mg) was treated in the same manner as described in Preparation Example 3 to give the title compound. Yield: 717 mg (theoretical amount).

Example 12

Synthesis of 4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl] methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:

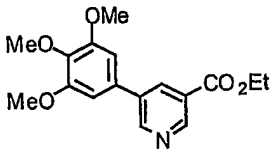


4-(*p*-Anisidino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (139 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder. Yield: 13 mg (5%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.76 (br, 2H), 1.88 (br, 2H), 2.14 (br, 2H), 2.97 (br, 2H), 3.51 (br, 1H), 3.57 (s, 2H), 3.73 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 6H), 3.96 (s, 6H), 4.42 (s, 2H), 6.78 (br, 4H), 7.20 (br, 3H), 7.23 (s, 2H), 7.57-7.70 (m, 3H), 8.58-8.60 (m, 2H).

Preparation Example 46

Synthesis of ethyl 5-(3,4,5-trimethoxyphenyl)nicotinate:



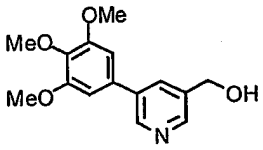
3,4,5-Trimethoxyphenylboronic acid (6.36 g) and ethyl 5-bromonicotinate (6.90 g) were reacted in the same manner as described in Preparation Example 1 to give the title compound.

Yield: 7.19 g (76%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.44 (t, 3H, J=7.1 Hz), 3.91 (s, 3H), 3.95 (s, 6H), 4.46 (q, 2H, J=7.1 Hz), 6.79 (s, 2H), 8.44 (t, 1H, J=2.1 Hz), 8.96 (d, 1H, J=2.1 Hz), 9.18 (d, 1H, J=1.8 Hz).

Preparation Example 47

Synthesis of 3-hydroxymethyl-5-(3,4,5-trimethoxyphenyl)pyridine:



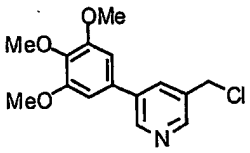
Ethyl 5-(3,4,5-trimethoxyphenyl)nicotinate (7.19 g) was treated in the same manner as described in the Preparation Example 2 to give the title compound.

Yield; 3.83 g (61%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.88 (s, 3H), 3.89 (s, 6H), 4.39 (br, 1H), 4.80 (s, 2H), 6.72 (s, 2H), 7.89 (t, 1H, J=1.2 Hz), 8.47 (d, 1H, J=2.1 Hz), 8.63 (d, 1H, J=2.2 Hz).

Preparation Example 48

Synthesis of 3-chloromethyl-5-(3,4,5-trimethoxyphenyl)pyridine:



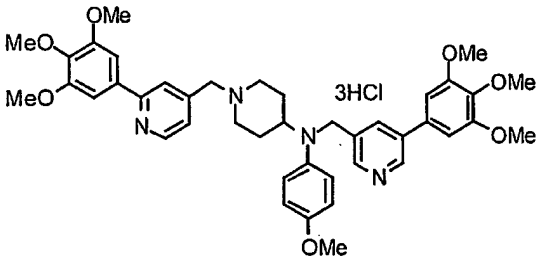
3-Hydroxymethyl-5-(3,4,5-trimethoxyphenyl)pyridine (2.85 g) was treated in the same manner as described in Preparation Example 3 to give the title compound.

Yield: 1.97 g (65%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 3.90 (s, 3H), 3.94 (s, 6H), 4.67 (s, 2H), 6.75 (s, 2H), 7.87 (t, 1H, J=2.1 Hz), 8.59 (d, 1H, J=2.0 Hz), 8.76 (d, 1H, J=2.1 Hz).

Example 13

Synthesis of 4-[N-(4-methoxyphenyl)-N-[[5-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:

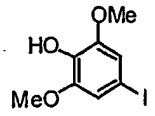


4-(*p*-Anisidino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (139 mg) and 3-chloromethyl-5-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder. Yield: 14 mg (5%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ: 1.73-1.75 (m, 2H), 1.88 (d, 2H, J=11.3 Hz), 2.13 (t, 2H, J=11.3 Hz), 2.96 (d, 2H, J=11.5 Hz), 3.50 (br, 1H), 3.55 (s, 2H), 3.72 (s, 3H), 3.88 (s, 3H), 3.89 (s, 9H), 3.96 (s, 6H), 4.45 (s, 2H), 6.65 (s, 2H), 6.76 (d, 2H, J=9.6 Hz), 6.80 (d, 2H, J=9.4 Hz), 7.20 (d, 1H, J=5.3 Hz), 7.22 (s, 2H), 7.59 (s, 1H), 7.67 (s, 1H), 8.50 (s, 1H), 8.59 (d, 1H, J=4.7 Hz), 8.62 (s, 1H).

Preparation Example 49

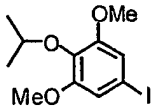
Synthesis of 2,6-dimethoxy-4-iodophenol:



To a solution of 5-iodo-1,2,3-trimethoxybenzene (3.2 g) in 1,2-dichloroethane (40 mL) was added aluminum chloride (1.6 g). The mixture was stirred at 60°C for 4 hours and evaporated. The residue was dissolved in 1 M aqueous sodium hydroxide solution and washed with ether. The aqueous layer was

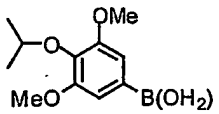
then acidified and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated to give the title compound as white crystalline powder.
Yield: 1.0 g (31%)

Preparation Example 50
Synthesis of 1,3-dimethoxy-5-iodo-2-isopropoxybenzene:



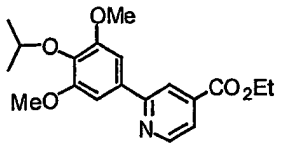
To a suspension of 2,6-dimethoxy-4-iodophenol (1.0 g) and potassium carbonate (938 mg) in DMF (10 mL) was added isopropyl iodide (507μL). The mixture was stirred at 60°C for 3 hours and evaporated. Ethyl acetate and water were added to the residue, the organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and evaporated. The residue was applied to a column of silica gel using hexane-ethyl acetate (5:1) as an eluent to give the title compound.
Yield: 788 mg (72%).

Preparation Example 51
Synthesis of 3,5-dimethoxy-4-isopropoxyphenylboronic acid:



1,3-Dimethoxy-5-iodo-2-isopropoxybenzene (2.25 g) was treated in the same manner as described in Preparation Example 27 to give the title compound.
Yield: 1.23 g (74%).

Preparation Example 52
Synthesis of ethyl 2-(3,5-dimethoxy-4-isopropoxyphenyl)isonicotinate:



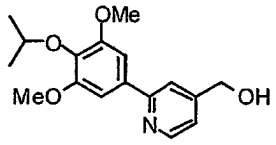
To a solution of 3,5-dimethoxy-4-isopropoxyphenylboronic acid (1.23 g) and ethyl 2-chloroisonicotinate (0.95 g) were condensed in the same manner as described in Preparation Example 1 to give the title compound.

Yield: 1.57 g(89%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.33 (d, 6H, J=4.9 Hz), 1.44 (t, 3H, J=7.1 Hz), 3.95 (s, 6H), 4.42-4.49 (m, 3H), 7.29 (s, 2H), 7.75 (dd, 1H, J=4.9 Hz, 1.4 Hz), 8.24 (s, 1H), 8.80 (d, 1H, J=4.9 Hz).

Preparation Example 53

Synthesis of 2-(3,5-dimethoxy-4-isopropoxyphenyl)-4-hydroxymethylpyridine:



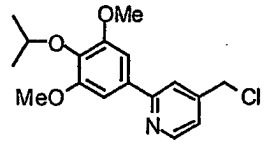
Ethyl 2-(3,5-dimethoxy -4-isopropoxyphenyl)isonicotinate (1.57 g) was treated in the same manner as described in the Preparation Example 2 to give the title compound.

Yield: 1.27 g (92%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (d, 6H, J=6.1 Hz), 3.93 (s, 6H), 4.45 (quint, 1H, J=6.1 Hz), 4.81 (s, 2H), 7.20 (d, 1H, J=5.1 Hz), 7.23 (s, 2H), 7.68 (s, 1H), 8.62 (d, 1H, J=5.1 Hz).

Preparation Example 54

Synthesis of 4-chloromethyl-2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridine:



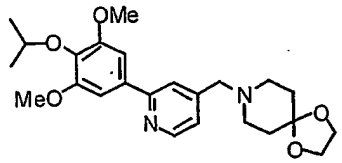
2-(3,5-Dimethoxy-4-isopropoxyphenyl)-4-hydroxymethylpyridine (1.49 g) was treated in the same manner as described in Preparation Example 3 to give the title compound.

Yield: 1.33 g (84%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (d, 6H, J=6.2 Hz), 3.94 (s, 6H), 4.45 (quint, 1H, J=6.1 Hz), 4.61 (s, 2H), 7.23-7.26 (m, 3H), 7.69 (s, 1H), 8.66 (d, 1H, J=5.1 Hz).

Preparation Example 55

Synthesis of 1-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl] -4-piperidone ethylene ketal:



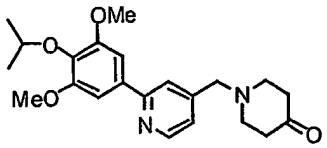
4-Chloromethyl-2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridine (643 mg) and 4-piperidone ethylene ketal (287 mg) were coupled in the same manner as described in Example 2 to give the title compound.

Yield: 818 mg (95%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.32 (d, 6H, J=6.1 Hz), 1.78 (t, 4H, J=5.7 Hz), 2.57 (br, 4H), 3.49 (s, 4H), 3.59 (s, 2H), 3.94 (s, 6H), 4.44 (quint, 1H, J=6.1 Hz), 7.21 (d, 1H, J=5.1 Hz), 7.23 (s, 2H), 7.65 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Preparation Example 56

Synthesis of 1-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl] -4-piperidone:



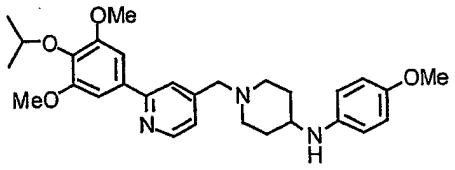
1-[[2-(3,5-Dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl]-4-piperidone ethylene ketal (818 mg) was treated in the same manner as described in Preparation Example 23 to give the title compound.

Yield: 717 mg (98%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (d, 6H, J=6.2 Hz), 2.50 (t, 4H, J=6.1 Hz), 2.81 (t, 4H, J=6.1 Hz), 3.69 (s, 2H), 3.95 (s, 6H), 4.45 (quint, 1H, J=6.2 Hz), 7.24 (s, 2H), 7.25-7.27 (m, 1H), 7.68 (s, 1H), 8.63 (d, 1H, J=5.1 Hz).

Preparation Example 57

Synthesis of 4-(*p*-anisidino)-1-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin -4-yl] methyl]piperidine:



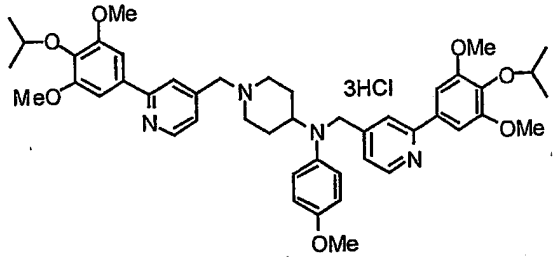
1-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (350 mg) and *p*-anisidine (123 mg) were condensed in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 307 mg (69%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (d, 6H, J=6.3 Hz), 1.46-1.52 (m, 2H), 2.00-2.24 (m, 2H), 2.22 (t, 2H, J=11.1 Hz), 2.86 (d, 2H, J=12.1 Hz), 3.18-3.28 (m, 1H), 3.58 (s, 2H), 3.74 (s, 3H), 3.94 (s, 6H), 4.40 (quint, 1H, J=6.3 Hz), 6.58 (d, 2H, J=6.6 Hz), 6.78 (d, 2H, J=6.6 Hz), 7.20 (d, 1H, J=5.1 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Example 14

Synthesis of 1-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl]-4- [N-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl) amino]piperidine trihydrochloride:



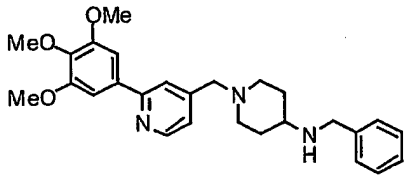
4-(*p*-anisidino)-1-[[2-(3,5-dimethoxy-4-isopropoxyphenyl)pyridin-4-yl]methyl] piperidine (307 mg) and 4-chloromethyl-2-(3,5-dimethoxy-4-isopropoxyphenyl) pyridine (201 mg) were condensed in the same manner as described in Example 9. A free base obtained was converted to a trihydrochloride giving the title compound as yellow powder.

Yield: 230 mg (46%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31 (d, 6H, J=3.3 Hz), 1.32 (d, 6H, J=6.8 Hz), 1.70-1.92 (m, 4H), 2.10-2.20 (m, 2H), 2.92-3.01 (m, 2H), 3.56 (s, 2H), 3.73 (s, 3H), 3.85-3.95 (m, 1H), 3.90 (s, 6H), 3.93 (s, 6H), 4.39-4.49 (m, 4H), 6.73 (d, 2H, J=4.8 Hz), 6.78 (d, 2H, J=4.8 Hz), 7.14 (s, 2H), 7.15-7.20 (m, 2H), 7.23 (s, 2H), 7.58 (s, 1H), 7.60 (s, 1H), 8.53 (d, 1H, J=5.1 Hz), 8.58 (d, 1H, J=5.1 Hz).

Preparation Example 58

Synthesis of 4-benzylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]-methyl] piperidine:



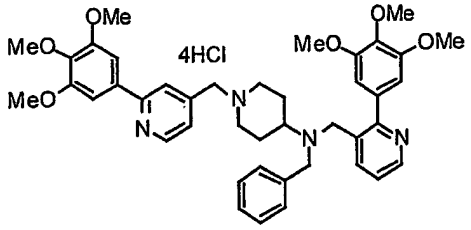
1-[[2-(3,4,5-Trimethoxyphenyl)pyridin-4-yl]methyl-4-piperidone (1.40 g) and benzylamine (0.51 g) was condensed in the same manner as described in Preparation Example 37 to give the title compound as yellow amorphous.

Yield: 1.20 g (68%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.40-1.60 (m, 2H), 1.88-2.09 (m, 5H), 2.54 (br, 1H), 2.82-2.85 (m, 2H), 3.52 (s, 2H), 3.80 (s, 2H), 3.89 (s, 3H), 3.95 (s, 6H), 7.18-7.31 (m, 8H), 7.64 (s, 1H), 8.57 (d, 1H, J=5.1 Hz).

Example 15

Synthesis of 4-[N-benzyl-N-[[2-(3,4,5-trimethoxypheny)pyridin-3-yl]-methyl]amino] -1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



4-Benzylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (134 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. A free base obtained was converted

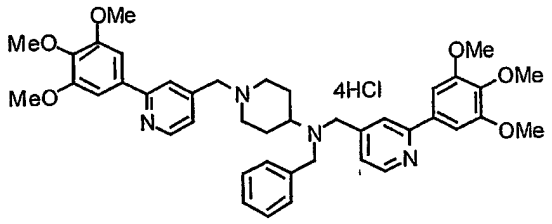
to a tetrahydrochloride to give the title compound as yellow powder.

Yield: 43 mg, (17%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.63 (br, 4H), 1.87 (br, 2H), 2.39 (br, 1H), 2.88 (br, 2H), 3.49 (s, 2H), 3.57 (s, 2H), 3.68 (s, 2H), 3.86 (s, 6H), 3.88 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 6.60 (s, 2H), 7.17 (d, 1H, J=5.1 Hz), 7.22-7.29 (m, 8H), 7.56 (s, 1H), 8.02 (d, 1H, J=8.0 Hz), 8.50 (d, 1H, J=6.4 Hz), 8.58 (d, 1H, J=5.1 Hz).

Example 16

Synthesis of 4-[N-benzyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino] -1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



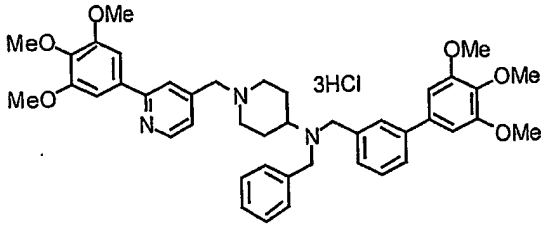
4-Benzylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (230 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (158 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a tetrahydrochloride which gave the title compound as yellow powder.

Yield: 172 mg (47%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.69-1.85 (m, 4H), 1.93-1.99 (m, 2H), 2.56 (br, 1H), 2.93-3.00 (m, 2H), 3.51 (s, 2H), 3.71 (s, 2H), 3.74 (s, 2H), 3.90 (s, 6H), 3.96 (s, 6H), 7.18-7.32 (m, 9H), 7.38 (d, 2H, J=7.1 Hz), 7.59 (s, 1H), 7.68 (s, 1H), 8.56 (d, 1H, J=5.1 Hz), 8.60 (d, 1H, J=5.1 Hz).

Example 17

Synthesis of 4-[N-benzyl-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2 -(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



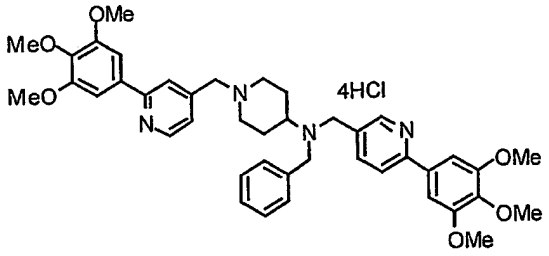
4-Benzylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (134 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder.

Yield: 47 mg (18%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.70-1.86 (m, 4H), 1.96 (br, 2H), 2.59 (br, 1H), 2.94 (br, 2H), 3.51 (s, 2H), 3.70 (s, 2H), 3.74 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.96 (s, 6H), 6.75 (s, 2H), 7.18-7.30 (m, 6H), 7.35-7.40 (m, 5H), 7.56 (s, 1H), 7.60 (s, 1H), 8.58 (d, 1H, J=5.1 Hz).

Example 18

Synthesis of 4-[N-benzyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1- [[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



4-Benzylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (134 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a tetrahydrochloride which gave the title compound as yellow powder.

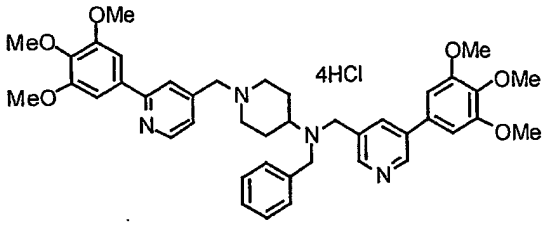
Yield: 44 mg (17%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ: 1.81 (br, 4H), 1.96 (br, 2H), 2.55 (br, 1H), 2.96 (br, 2H), 3.52 (s, 2H), 3.69 (s, 4H), 3.89 (s, 6H), 3.95 (s, 6H), 3.96 (s, 6H), 7.19-7.32 (m, 8H), 7.36-7.38 (m, 2H), 7.61 (d, 2H, J=7.6 Hz), 7.69-7.73 (m,

1H), 8.59 (d, 1H, J=4.9 Hz), 8.63 (s, 1H).

Example 19

Synthesis of 4-[N-benzyl-N-[[5-(3,4,5-trimethoxypheny)pyridin-3-yl]methyl] amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



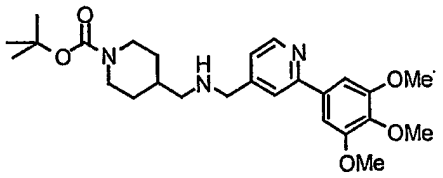
4-Benzylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (134 mg) and 3-chloromethyl-5-(3,4,5-trimethoxyphenyl)pyridine (114mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a tetrahydrochloride which gave the title compound as yellow powder.

Yield: 26 mg (10%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ: 1.83 (br, 4H), 1.97 (br, 2H), 2.58 (br, 1H), 2.95 (br, 2H), 3.53 (s, 2H), 3.71 (s, 2H), 3.75 (s, 2H), 3.90 (s, 6H), 3.93 (s, 6H), 3.96 (s, 6H), 6.74 (s, 2H), 7.19-7.30 (m, 6H), 7.36 (d, 2H, J=6.8 Hz), 7.60 (s, 1H), 7.79 (s, 1H), 8.54 (s, 1H), 8.59 (d, 1H, J=5.1 Hz), 8.64 (s, 1H).

Preparation Example 59

Synthesis of 1-(*tert*-butoxycarbonyl)-4-[N-[[2-(3,4,5-trmethoxyphenyl)pyridin-4 -yl]methyl]aminomethyl]piperidine:



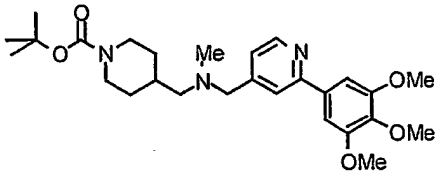
1-(*tert*-Butoxycarbonyl)-4-aminomethylpiperidine (200mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (183mg) were condensed in the same manner as described in Example 2 to give the title compound as yellow syrup.

Yield: 264 mg (90%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.12-1.27 (m, 3H), 1.45 (s, 9H), 1.60 (br, 1H), 1.74 (d, 2H, J=12.9 Hz), 2.54 (d, 2H, J=6.6 Hz), 2.69 (br, 2H), 3.87 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 4.03-4.14 (m, 2H), 7.20 (d, 1H, J=3.9 Hz), 7.24 (s, 2H), 7.65 (s, 1H), 8.60 (d, 1H, J=4.9 Hz).

Preparation Example 60

Synthesis of 1-(*tert*-butoxycarbonyl)-4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl]methyl]aminomethyl]piperidine:



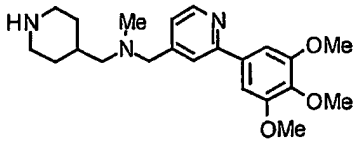
1-(*tert*-butoxycarbonyl)-4-[N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]aminomethyl]piperidine (264 mg) was treated in the same manner as described in PreparationExample 11 to give the title compound as yellow syrup.

Yield: 157 mg (58%).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 1.00-1.09 (m, 2H), 1.43 (s, 9H), 1.65-1.70 (m, 1H), 1.79 (d, 2H, J=12.7 Hz), 2.21 (d, 2H, J=7.4 Hz), 2.23 (s, 3H), 2.69 (br, 2H), 3.52 (s, 2H), 3.89 (s, 3H), 3.96 (s, 6H), 4.07-4.13 (m, 2H), 7.20 (d, 1H, J=4.9 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.58 (d, 1H, J=5.1 Hz).

Preparation Example 61

Synthesis of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] aminomethyl] piperidine:



1-(*tert*-Butoxycarbonyl)-4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]aminomethyl]piperidine (152 mg) was treated in the same manner as

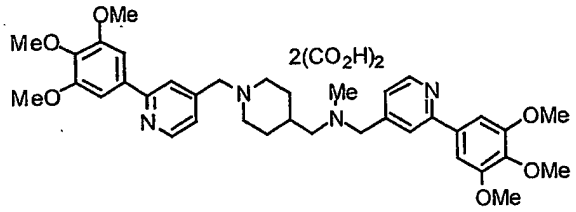
described in Preparation Example 12 to give the title compound as yellow crystals.

Yield: 105 mg (88%).

^{1}H-NMR (400MHz, $CDCl_3$) δ: 1.00-1.10 (m, 2H), 1.60-1.68 (m, 1H), 1.80 (d, 2H, J=12.5 Hz), 2.03 (br, 1H), 2.20 (d, 2H, J=8.4 Hz), 2.21 (s, 3H), 2.58 (dt, 2H, J=12.1 Hz, 2.1 Hz), 3.05 (d, 2H, J=12.1 Hz), 3.51 (s, 2H), 3.89 (s, 3H), 3.95 (s, 6H), 7.20 (d, 1H, J=5.1 Hz), 7.24 (s, 2H), 7.65 (s, 1H), 8.57 (d, 1H, J=5.9 Hz).

Example 20

Synthesis of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] aminomethyl]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dioxalate:



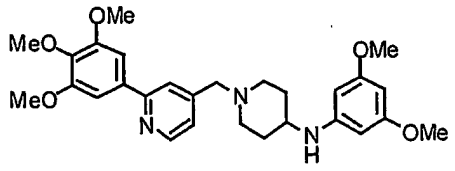
4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino-methyl] piperidine (96 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (73 mg) were condensed in the same manner as described in Example 2. The title compound was obtained as white powder after converting a free base to a dioxalate.

Yield: 109 mg (40%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.19-1.27 (m, 2H), 1.56 (br, 1H), 1.81 (d, 2H, J=11.1 Hz), 1.99-2.04 (m, 2H), 2.23 (s, 5H), 2.88 (d, 2H, J=11.1 Hz), 3.53 (s, 4H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 6H), 3.96 (s, 6H), 7.20 (br, 2H), 7.23 (s, 4H), 7.61 (s, 1H), 7.64 (s, 1H), 8.58 (d, 2H, J=4.9 Hz).

Preparation Example 62

Synthesis of 4-(3,5-dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



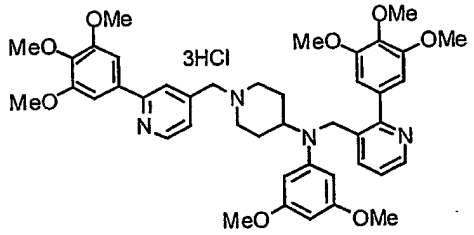
1-[[2-(3,4,5-Trimethoxyphenyl)pyridin-4-yl]methyl-4-piperidone (1.40 g) and 3,5-dimethoxyaniline (722 mg) were treated in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 800 mg (41%).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 1.40-1.90 (m, 2H), 1.95-2.50 (m, 4H), 2.93 (br, 2H), 3.31 (br, 1H), 3.65 (br, 2H), 3.72 (s, 6H), 3.88 (s, 3H), 3.96 (s, 6H), 5.76 (s, 2H), 5.85 (s, 1H), 7.20-7.35 (m, 3H), 7.73 (br, 1H), 8.60 (d, 1H, J=4.9 Hz).

Example 21

Synthesis of 4-[N-(3,5-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



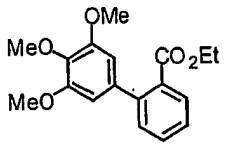
4-(3,5-Dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (148 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. Yellow syrup obtained was converted to a trihydrochloroide to give the title compound as yellow powder.

Yield: 29 mg, (11%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.60-1.63 (m, 2H), 1.79 (d, 2H, J=11.7 Hz), 2.13 (t, 2H, J=11.4 Hz), 2.94 (d, 2H, J=11.3 Hz), 3.54 (s, 2H), 3.71 (s, 6H), 3.78-3.84 (m, 1H), 3.90 (s, 3H), 3.91 (s, 6H), 3.92 (s, 3H), 3.96 (s, 6H), 4.41 (s, 2H), 5.84 (s, 2H), 6.72 (s, 2H), 7.09-7.24 (m, 5H), 7.53 (s, 1H), 7.71 (d, 1H, J=6.6 Hz), 8.51 (dd, 1H, J=4.7 Hz, 1.6 Hz), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 63

Synthesis of ethyl 2-(3,4,5-trimethoxyphenyl)benzoate:



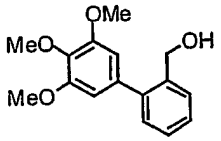
3,4,5-Trimethoxyphenylboronic acid (639 mg) and ethyl 2-bromobenzoate (479 mg) were condensed in the same manner as described in Preparation Example 1 to give the title compound.

Yield: 655 mg (69%).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 1.04 (t, 3H, J=7.2 Hz), 3.86 (s, 6H), 3.89 (s, 3H), 4.12 (q, 2H, J=7.2 Hz), 6.54 (s, 2H), 7.40-7.42 (m, 2H), 7.51 (t, 1H, J=7.8 Hz), 7.77 (d, 1H, J=6.8 Hz).

Preparation Example 64

Synthesis of 2-(3,4,5-trimethoxyphenyl)benzyl alcohol:



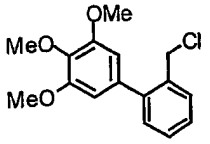
Ethyl 2-(3,4,5-trimethoxyphenyl)benzoate (655 mg) was treated in the same manner as described in Preparation Example 2 to give the title compound.

Yield: 630 mg (theoretical amount).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 3.85 (s, 6H), 3.90 (s, 3H), 4.61 (s, 2H), 6.61 (s, 2H), 7.26-7.39 (m, 3H), 7.53 (d, 1H, J=6.8 Hz).

Preparation Example 65

Synthesis of 2-(3,4,5-trimethoxyphneyl)benzyl chloride:



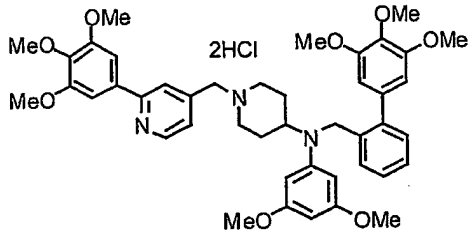
2-(3,4,5-Trimethoxyphenyl)benzyl alcohol (630 mg) was treated in the same manner as described in Preparation Example 3 to give the title compound.

Yield: 615 mg (theoretical amount).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 3.87 (s, 6H), 3.90 (s, 3H), 4.53 (s, 2H), 6.66 (s, 2H), 7.29-7.32 (m, 1H), 7.34-7.39 (m, 2H), 7.50-7.52 (m, 1H).

Example 22

Synthesis of 4-[N-(3,5-dimethoxyphenyl)-N-[2-(3,4,5-trimethoxyphenyl)benzyl] amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



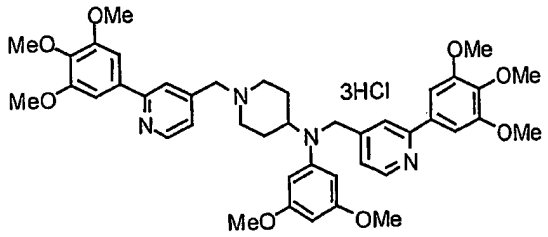
4-(3,5-Dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]piperidine (148 mg) and 2-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. A free base obtained was converted to a dihydrochloroide to give the title compound as yellow powder.

Yield: 20 mg, (8%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.50-1.90 (m, 4H), 2.05-2.20 (m, 2H), 2.92 (br, 2H), 3.52 (br, 3H), 3.68 (s, 6H), 3.85 (s, 6H), 3.88 (s, 3H), 3.89 (s, 3H), 3.94 (s, 6H), 4.31 (s, 2H), 5.85 (br, 3H), 6.52 (s, 2H), 7.05-7.27 (m, 6H), 7.34 (s, 1H), 7.51 (s, 1H), 8.56 (s, 1H).

Example 23

Synthesis of 4-[N-(3,5-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



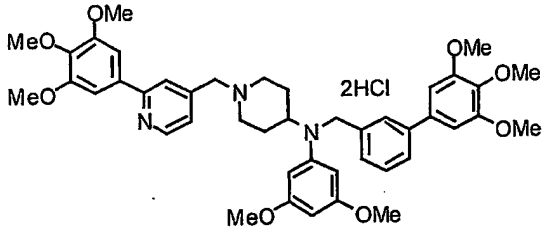
4-(3,5-Dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (148 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder.

Yield: 40 mg (18%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.68-1.90 (m, 4H), 2.12-2.22 (m, 2H), 2.94-3.02 (m, 2H), 3.57 (s, 2H), 3.71 (s, 6H), 3.81-3.83 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.52 (s, 2H), 5.89-5.94 (m, 3H), 7.14 (d, 1H, J=5.3 Hz), 7.16 (s, 2H), 7.20 (d, 1H, J=3.7 Hz), 7.22 (s, 2H), 7.54-7.60 (m, 2H), 8.55 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=5.1 Hz).

Example 24

Synthesis of 4-[N-(3,5-dimethoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



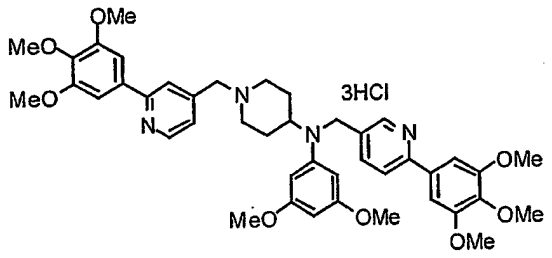
4-(3,5-Dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (148 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a dihydrochloride which gave the title compound as yellow powder.

Yield: 41 mg (16%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.78-1.88 (m, 4H), 2.16 (t, 2H, J=10.7 Hz), 2.96 (d, 2H, J=11.3 Hz), 3.56 (s, 2H), 3.70 (s, 6H), 3.73-3.84 (m, 1H), 3.87 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.95 (s, 6H), 4.54 (s, 2H), 5.95 (s, 2H), 6.71 (s, 2H), 7.19-7.26 (m, 4H), 7.31-7.39 (m, 3H), 7.42 (s, 1H), 7.59 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 25

Synthesis of 4-[N-(3,5-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



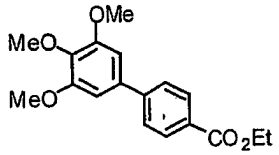
4-(3,5-Dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (148 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder.

Yield: 23 mg (10%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.64 (br, 2H), 1.82 (br, 2H), 2.10 (br, 2H), 2.94 (br, 2H), 3.48-3.60 (m, 3H), 3.64 (s, 6H), 3.82 (s, 3H), 3.83 (s, 3H), 3.87 (s, 6H), 3.90 (s, 6H), 4.46 (s, 2H), 5.85 (br, 3H), 7.05-7.24 (m, 6H), 7.53-7.54 (m, 2H), 8.51 (s, 1H), 8.54 (br, 1H).

Preparation Example 66

Synthesis of ethyl 4-(3,4,5-trimethoxyphenyl)benzoate:



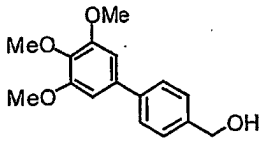
3,4,5-Trimethoxyphenylboronic acid (2.01 g) and ethyl 4-bromobenzoate (2.29 g) were condensed in the same manner as described in Preparation Example 1 to give the title compound.

Yield: 2.99 g (95%).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 1.42 (t, 3H, J=7.2 Hz), 3.90 (s, 3H), 3.94 (s, 6H), 4.38 (q, 2H, J=7.2 Hz), 6.81 (s, 2H), 7.62 (d, 2H, J=8.2 Hz), 8.10 (d, 2H, J=8.2 Hz).

Preparation Example 67

Synthesis of 4-(3,4,5-trimethoxyphenyl)benzyl alcohol:

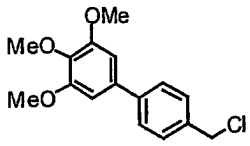


Ethyl 4-(3,4,5-trimethoxyphenyl)benzoate (2.99 g) was treated in the same manner as described in Preparation Example 2 to give the title compound.

Yield: 1.83 g (71%)

Preparation Example 68

Synthesis of 4-(3,4,5-trimethoxyphenyl)benzyl chloride:



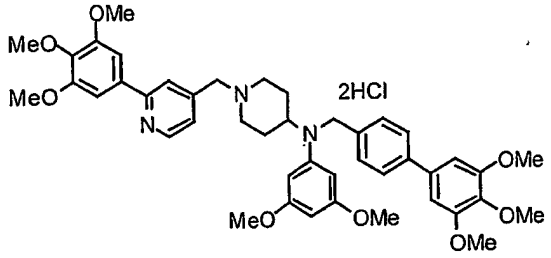
4-(3,4,5-Trimethoxyphenyl)benzyl alcohol (1.83 g) was treated in the same manner as describe in Preparation Example 3 to give the title compound.

Yield: 1.65 g (84%)

^{1}H-NMR (400MHz, $CDCl_3$) δ : 3.90 (s, 3H), 3.93 (s, 6H), 4.65 (s, 2H), 6.77 (s, 2H), 7.46 (d, 2H, J=8.0 Hz), 7.55 (d, 2H, J=8.0 Hz).

Example 26

Synthesis of 4-[N-(3,5-dimethoxyphenyl)-N-[4-(3,4,5-trimethoxypheny)benzyl] amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



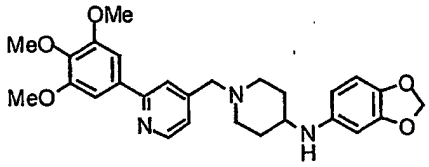
4-(3,5-Dimethoxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (148 mg) and 4-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a dihydrochloride which gave yellow powder of the title compound.

Yield: 35 mg (14%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ ; 1.80-1.89 (m, 4H), 2.17 (br, 2H), 2.97 (d, 2H, J=10.5 Hz), 3.57 (s, 2H), 3.70 (s, 6H), 3.77-3.84 (m, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.96 (s, 6H), 4.52 (s, 2H), 5.93 (s, 2H), 6.74 (s, 2H), 7.19-7.22 (m, 4H), 7.31 (d, 2H, J=8.2 Hz), 7.46 (d, 2H, J=8.2 Hz), 7.60 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Preparation Example 69

Synthesis of 4-(3,4-methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl]methyl]piperidine:



1-[[2-(3,4,5-Trimethoxyphenyl)pyridin-4-yl]methyl-4-piperidone (1.40 g) and 3,4-methylenedioxyaniline (646 mg) were treated in the same manner as described in Preparation Example 29 to give the title compound.

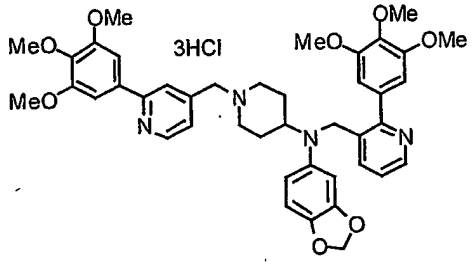
Yield: 810 mg (43%).

^{1}H-NMR (400MHz, $CDCl_3$) δ : 1.63 (br, 2H), 2.02-2.60 (m, 4H), 2.80-3.15 (m, 2H),

3.25 (br, 1H), 3.70 (br, 2H), 3.88 (s, 3H), 3.96 (s, 6H), 5.83 (s, 2H), 6.02 (d, 1H, J=8.3 Hz), 6.22 (s, 1H), 6.61 (d, 1H, J=8.3 Hz), 7.18-7.28 (m, 3H), 7.64 (br, 1H), 8.60 (d, 1H, J=4.9 Hz).

Example 27

Synthesis of 4-[N-(3,4-methylenedioxyphenyl)-N-[[2-(3,4,5-trimethoxypheny) pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] piperidine trihydrochloride:



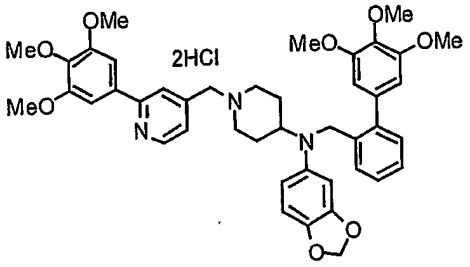
4-(3,4-Methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (119 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. Yellow syrup obtained was converted to a trihydrochloroide to give the title compound as yellow powder.

Yield: 30 mg (14%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.45-2.25 (m, 6H), 2.90 (br, 2H), 3.40 (br, 1H), 3.55 (br, 2H), 3.87 (s, 3H), 3.88 (s, 9H), 3.93 (s, 6H), 4.28 (s, 2H), 5.82 (s, 2H), 6.10 (br, 1H), 6.28 (s, 1H), 6.58 (d, 1H, J=8.4 Hz), 6.67 (s, 2H), 7.12-7.30 (m, 4H), 7.52 (br, 1H), 7.75 (br, 1H), 8.51 (br, 1H), 8.57 (br, 1H).

Example 28

Synthesis of 4-[N-(3,4-methylenedioxyphenyl)-N-[2-(3,4,5-trimethoxyphenyl) benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]metyl]piperidine dihydrochloride:



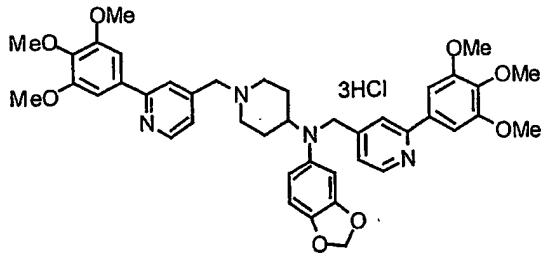
4-(3,4-Methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (119 mg) and 2-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. A free base obtained was converted to a dihydrochloroide to give the title compound as yellow powder.

Yield: 13 mg (6%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.61 (br, 2H), 1.78 (br, 2H), 2.10 (br, 2H), 2.91 (br, 2H), 3.50-3.54 (m, 3H), 3.87 (s, 6H), 3.90 (s, 3H), 3.92 (s, 3H), 3.99 (s, 6H), 4.26 (s, 2H), 5.82 (s, 2H), 6.12 (d, 1H, J=8.6 Hz), 6.32 (s, 1H), 6.53 (s, 2H), 6.62 (d, 1H, J=8.6 Hz), 7.17-7.26 (m, 6H), 7.42 (br, 1H), 7.55 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 29

Synthesis of 4-[N-(3,4-methylenedioxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl) pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] piperidine trihydrochloride:



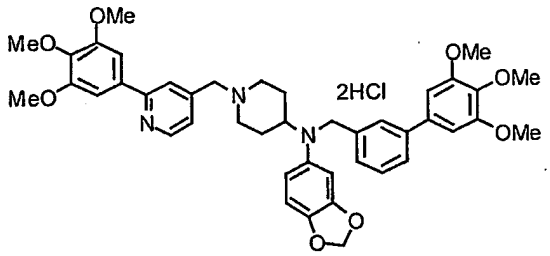
4-(3,4-Methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]piperidine (119 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl) pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder.

Yield: 52 mg (25%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.60-1.95 (m, 4H), 2.20 (br, 2H), 3.00 (br, 2H), 3.58 (br, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 3.94 (s, 6H), 4.41 (s, 2H), 5.82 (s, 2H), 6.17 (d, 1H, J=8.4 Hz), 6.39 (s, 1H), 6.62 (d, 1H, J=8.4 Hz), 7.12-7.13 (m, 3H), 7.18 (d, 1H, J=4.1 Hz), 7.23 (br, 2H), 7.54 (br, 2H), 8.51 (d, 1H, J=5.1 Hz), 8.57 (d, 1H, J=4.9 Hz).

Example 30

Synthesis of 4-[N-(3,4-methylenedioxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl) benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



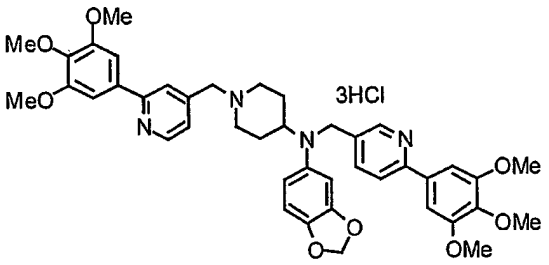
4-(3,4-Methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (119 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a dihydrochloride which gave the title compound as yellow powder.

Yield: 58 mg (29%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.60-1.97 (m, 4H), 2.15 (br, 2H), 3.00 (br, 2H), 3.58 (br, 3H), 3.86 (s, 3H), 3.88 (s, 9H), 3.94 (s, 6H), 4.43 (s, 2H), 5.81 (s, 2H), 6.21 (br, 1H), 6.42 (s, 1H), 6.62 (d, 1H, J=8.4 Hz), 6.69 (s, 2H), 7.18 (d, 1H, J=4.9 Hz), 7.22-7.39 (m, 6H), 7.60 (br, 1H), 8.57 (d, 1H, J=4.9 Hz).

Example 31

Synthesis of 4-[N-(3,4-methylenedioxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl) pyridin-5-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl] piperidine trihydrochloride:



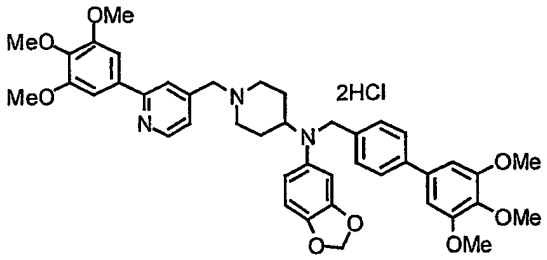
4-(3,4-Methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]piperidine (119 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl) pyridine (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a trihydrochloride which gave the title compound as yellow powder.

Yield: 69 mg (27%).

^{1}H-NMR (400MHz, measured as a free base, $CDCl_3$) δ : 1.71-1.88 (m, 4H), 2.14 (d, 2H, J=11.2 Hz), 2.97 (d, 2H, J=11.5 Hz), 3.45-3.52 (m, 1H), 3.56 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 6H), 3.96 (s, 6H), 4.12 (s, 2H), 5.85 (s, 2H), 6.24 (dd, 1H, J=8.5 Hz, 2.5 Hz), 6.45 (d, 1H, J=2.4 Hz), 6.64 (d, 1H, J=8.5 Hz), 7.20-7.21 (m, 1H), 7.21 (s, 2H), 7.23 (s, 2H), 7.58-7.65 (m, 3H), 8.57 (d, 1H, J=1.5 Hz), 8.59 (d, 1H, J=4.9 Hz).

Example 32

Synthesis of 4-[N-(3,4-Methylenedioxyphenyl)-N-[4-(3,4,5-trimethoxyphenyl) benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



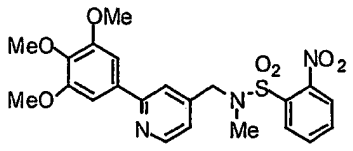
4-(3,4-Methylenedioxyphenylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl] methyl]piperidine (119 mg) and 4-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed by the same manner as described in Example 9. Yellow oil of a free base was converted to a dihydrochloride which gave the title compound as yellow powder.

Yield: 29 mg (14%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ ; 1.62-2.00 (m, 4H), 2.20 (br, 2H), 2.99 (br, 2H), 3.58 (br, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 6H), 4.41 (s, 2H), 5.82 (s, 2H), 6.19 (d, 1H, J=8.6 Hz), 6.39 (s, 1H), 6.63 (d, 1H, J=8.4 Hz), 6.72 (s, 2H), 7.18 (d, 1H, J=5.1 Hz), 7.23 (s, 2H), 7.29 (d, 2H, J=8.0 Hz), 7.43 (d, 2H, J=8.2 Hz), 7.60 (br, 1H), 8.57 (d, 1H, J=4.9 Hz).

Preparation Example 70

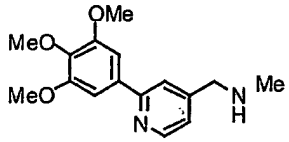
Synthesis of 4-[N-methyl-N-[(2-nitrobenzene)sulfonyl]aminomethyl]-2-(3,4,5-trimethoxyphenyl)pyridine:



4-Chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (232 mg), N-methyl-2-nitrobenzenesulfonamide (171mg) and potassium carbonate (138 mg) were suspended in acetonitrile (10 mL). The mixture was stirred at room temperature overnight and evaporated. To the residue was added chloroform and water. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate and evaporated to give the title compound.
Yield: 362 mg (97.0%).

Preparation Example 71

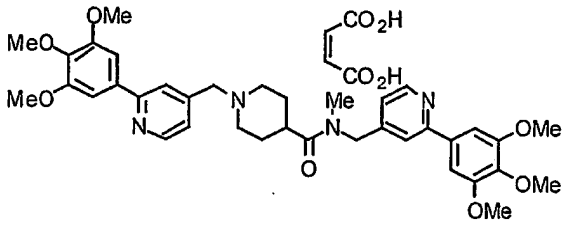
Synthesis of 4-(methylaminomethyl)-2-(3,4,5-trimethoxyphenyl)pyridine:



To a suspension of 4-[N-methyl-N-[(2-nitrobenzene)sulfonyl]aminomethyl]-2-(3,4,5-trimethoxyphenyl)pyridine (691 mg) and potassium carbonate (203 mg) in acetonitrile (20 mL) was added thiophenol (228μL). The mixture was stirred at 50°C overnight and evaporated. To the residue was added chloroform and water. The organic layer was separated, washed with saturated aqueous sodium hydrogencarbonate and brine, dried over anhydrous magnesium sulfate and evaporated. The residue was subjected to a column of silica gel using chloroform-methanol (40:1) and then chloroform-methanol (10:1) as eluents. Fractions containing the product were collected and evaporated to give the title compound.
Yield: 356 mg (84%).

Example 33

Synthesis of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]aminocarbonyl]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine maleate:



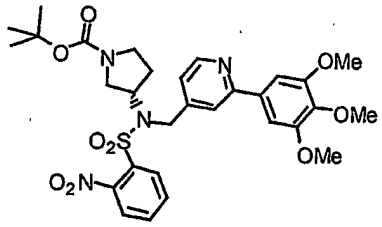
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine-4-caroxylic acid (98 mg) and 4-(methylaminomethyl)-2-(3,4,5-trimethoxyphenyl)pyridine (73 mg) were condensed by the same manner as described in Example 1 giving a maleate of the title compound as white powder.

Yield: 145 mg (75%).

^{1}H-NMR (400 MHz, measured as a maleate, DMSO-d_6)δ: 1.89-1.97 (m, 4H), 2.75-2.96 (m, 3H), 3.03 (s, 3H), 3.27 (d, 2H, J=12.0 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 3.87 (s, 6H), 3.90 (s, 6H), 4.09 (s, 2H), 4.64 (s, 2H), 6.14 (s, 2H), 7.09 (d, 1H, J=5.0 Hz), 7.33 (s, 2H), 7.37 (d, 1H, J=5.0 Hz), 7.38 (s, 2H), 7.65 (s, 1H), 7.90 (s, 1H), 8.57 (d, 1H, J=5.0 Hz), 8.67 (d, 1H, J=5.0 Hz).

Preparation Example 72

Synthesis of (3S)-1-(tert-butoxycarbonyl)-3-[N-[(2-nitrobenzene)sulfonyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]pyrrolidine:

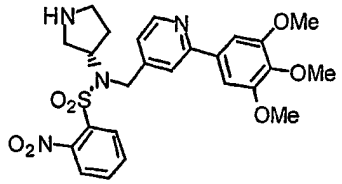


(3S)-1-(tert-Butoxycarbonyl)-3-[(2-nitrobenzene)sulfonylamino]pyrrolidine (72 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (57 mg) were condensed in the same manner as described in Example 2 to give colorless amorphous of the title compound.

Yield:103 mg (85%).

Preparation Example 73

Synthesis of (3S)-3-[N-[(2-nitrobenzene)sulfonyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]pyrrolidine:



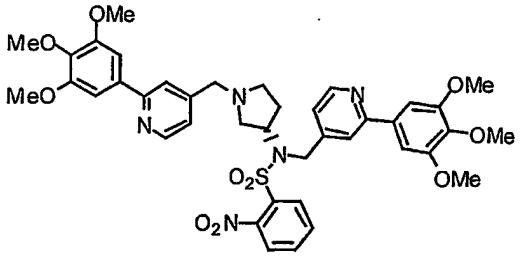
(3S)-1-(tert-butoxycarbonyl)-3-[N-[(2-nitrobenzene)sulfonyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]pyrrolidine (103 mg) was treated in the same manner as described in Preparation Example 12 to give yellow amorphous of the title compound.

Yield: 72 mg (84%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.66-1.75 (m, 1H), 2.03-2.05 (m, 1H), 2.78-2.85 (m, 2H), 3.00-3.10 (m, 2H), 3.39 (br, 1H), 3.90 (s, 3H), 3.96 (s, 6H), 4.59-4.67 (m, 1H), 4.70 (s, 2H), 7.13-7.18 (m, 1H), 7.20 (s, 2H), 7.52-7.64 (m, 4H), 7.95 (dd, 1H, J=7.9 Hz, 1.1 Hz), 8.52 (d, 1H, J=5.1 Hz).

Preparation Example 74

Synthesis of (3S)-3-[N-[(2-nitrobenzene)sulfonyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]pyrrolidine:



(3S)-3-[N-[(2-Nitrobenzene)sulfonyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]pyrrolidine (72 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (40 mg) were treated in the same manner as described in Example 2 to give a yellow amorphous of the title compound.

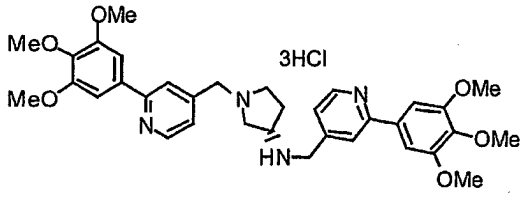
Yield: 97 mg (91%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.59 (br, 1H), 1.80-1.90 (m, 1H), 2.20-2.30 (m, 2H),

2.55 (dd, 1H, J=10.5 Hz, 8.2 Hz), 2.78 (dd, 1H, J=10.6 Hz, 3.2 Hz), 2.87 (t, 1H, J=7.2 Hz), 3.50 (d, 1H, J=13.7 Hz), 3.64 (d, 1H, J=13.7 Hz), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.83 (d, 2H, J=4.5 Hz), 7.07 (d, 1H, J=5.1 Hz), 7.10 (d, 1H, J=4.9 Hz), 7.15 (s, 2H), 7.17 (s, 2H), 7.41-7.45 (m, 1H), 7.50-7.55 (m, 3H), 7.61 (s, 1H), 7.81 (d, 1H, J=7.4 Hz), 8.45 (d, 1H, J=4.9 Hz), 8.51 (d, 1H, J=5.1 Hz).

Example 34

Synthesis of (3S)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-3-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methylamino]pyrrolidine trihydrochloride:

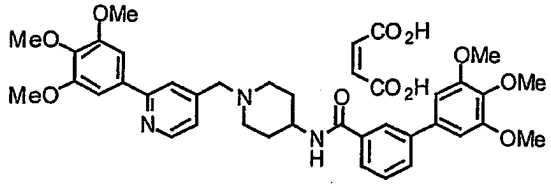


(3S)-3-[N-[(2-nitrobenzene)sulfonyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]pyrrolidine (97 mg) was treated in the same manner as described in Preparation Example 11 to give yellow amorphous of the title compound, which was converted to a trihydrochloride. Yield: 80mg (89%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.71 (br, 2H), 2.19-2.21 (m, 1H), 2.52-2.55 (m, 2H), 2.73-2.77 (m, 2H), 3.39 (br, 1H), 3.66 (d, 1H, J=13.7 Hz), 3.71 (d, 1H, J=13.7 Hz), 3.82 (s, 2H), 3.90 (s, 6H), 3.95 (s, 12H), 7.18-7.21 (m, 2H), 7.23 (s, 2H), 7.24 (s, 2H), 7.63 (s, 2H), 8.59 (d, 1H, J=4.3 Hz), 8.60 (d, 1H, J=4.3 Hz).

Example 35

Synthesis of 4-[3-(3,4,5-trimethoxyphenyl)benzoylamino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine maleate:



3-(3,4,5-trimethoxyphenyl)benzoic acid (69 mg) and 4-amino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (114 mg) were condensed in the same manner as described in Example 1. The title compound was obtained after converting

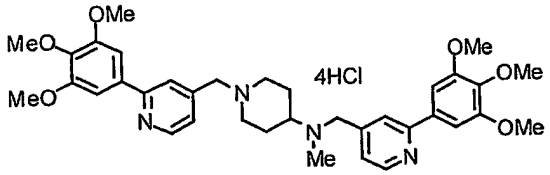
the product to a maleate.

Yield: 100 mg (56%)

^{1}H-NMR (400 MHz, measured as a maleate, DMSO-d_6)δ: 1.85-2.10 (m, 4H), 2.77-2.93 (m, 2H), 3.20-3.31 (m, 2H), 3.77 (s, 3H), 3.79 (s, 3H), 3.89 (s, 6H), 3.91 (s, 6H), 3.98-4.07 (m, 1H), 4.13 (s, 2H), 6.15 (s, 2H), 6.94 (s, 2H), 7.40-7.52 (m, 4H), 7.73-7.80 (m, 2H), 8.02-8.10 (m, 3H), 8.67-8.68 (m, 1H).

Example 36

Synthesis of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



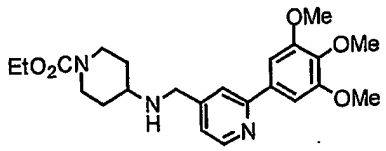
4-(methylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (2.67 g) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (2.12 g) were condensed in the same manner as described in Example 2. The title compound was obtained after converting a free base to a tetrahydrochloride.

Yield: 2.55 g (46%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.66-1.74 (m, 2H), 1.82 (d, 2H, J=10.7 Hz), 2.04 (t, 2H, J=11.0 Hz), 2.25 (s, 3H), 2.45-2.51 (m, 1H), 2.98 (d, 2H, J=11.7 Hz), 3.55 (s, 2H), 3.66 (s, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 3.96 (s, 6H), 3.97 (s, 6H), 7.21-7.23 (m, 2H), 7.24 (s, 2H), 7.25 (s, 2H), 7.62 (s, 1H), 7.63 (s, 1H), 8.59 (d, 1H, J=5.1 Hz), 8.60 (d, 1H, J=5.3 Hz).

Preparation Example 75

Synthesis of 1-(ethoxycarbonyl)-4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methylamino]piperidine:



4-Amino-1-(ethoxycarbonyl)piperidine (341 mg) and 4-chloromethyl-2-(3,4,5-

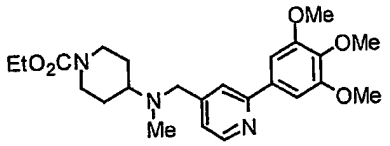
trimethoxyphenyl)pyridine (300 mg) were condensed in the same manner as described in Example 2 to give the title compound.

Yield: 438 mg (theoretical yield).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.25 (t, 3H, J=7.1 Hz), 1.27-1.34 (m, 2H), 1.60 (br, 1H), 1.90 (d, 2H, J=10.9 Hz), 2.67-2.72 (m, 1H), 2.87 (t, 2H, J=11.5 Hz), 3.90 (s, 3H), 3.91 (br, 2H), 3.96 (s, 6H), 4.09 (br, 2H), 4.12 (q, 2H, J=7.0 Hz), 7.21 (d, 1H, J=3.5 Hz), 7.24 (s, 2H), 7.65 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 76

Synthesis of 1-(ethoxycarbonyl)-4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



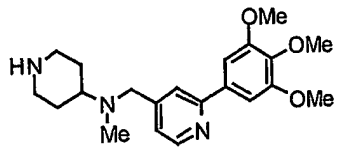
To a solution of 1-(ethoxycarbonyl)-4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methylamino]piperidine (438 mg) was treated in the same manner as described in Preparation Example 11 to give the title compound as yellow syrup.

Yield: 235mg (52%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.26 (t, 3H, J=7.1 Hz), 1.42-1.57 (m, 2H), 1.82 (d, 2H, J=11.9 Hz), 2.24 (s, 3H), 2.59-2.65 (m, 1H), 2.75 (t, 2H, J=12.0 Hz), 3.65 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 4.13 (q, 2H, J=7.0 Hz), 4.23 (br, 2H), 7,22 (dd, 1H, J=5.0 Hz, 1.3 Hz), 7.24 (s, 2H), 7.63 (s, 1H), 8.59 (d, 1H, J=4.5 Hz).

Preparation Example 77

Synthesis of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



To a solution of 1-(ethoxycarbonyl)-4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (100 mg) in ethanol (2 mL)

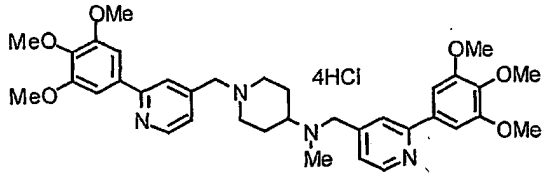
was added 4 M sodium hydroxide (8 mL). The mixture was refluxed overnight and extracted with chloroform. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to a column of silica gel and liquid chromatography was performed using chloroform-methanol (20:1) to give the title compound as yellow syrup.

Yield: 73 mg (88%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.50-1.55 (m, 2H), 1.84 (d, 2H, J=12.0 Hz), 1.99 (br, 1H), 2.25 (s, 3H), 2.55-2.63 (m, 3H), 3.16 (d, 2H, J=12.2 Hz), 3.65 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 7.22 (d, 1H, J=6.1 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.58 (d, 1H, J=5.1 Hz).

Example 37

Synthesis of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:

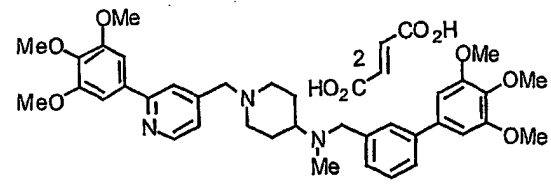


4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (73 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (58 mg) were condensed in the same manner as described in Example 2. The title compound was obtained after converting a free base to a tetrahydrochloride.

Yield: 126 mg (84%).

Example 38

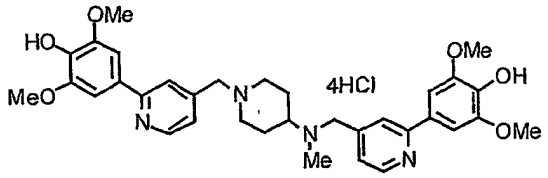
Synthesis of 4-[N-methyl-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine difumarate:



4-(methylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (111 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (88 mg)

were condensed in the same manner as described in Example 2. The title compound was obtained as white powder after converting a free base to a difumarate.
Yield: 59 mg (46%).
^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.70-1.77 (m, 2H), 1.85-1.87 (m, 2H), 2.03-2.08 (m, 2H), 2.27 (s, 3H), 2.55-2.59 (m, 1H), 2.98 (d, 2H, J=11.3 Hz), 3.56 (s, 2H), 3.69 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.98 (s, 6H), 6.79 (s, 2H), 7.22 (d, 1H, J=4.9 Hz), 7.28 (s, 2H), 7.31 (d, 1H, J=7.6 Hz), 7.38 (t, 1H, J=7.4 Hz), 7.45 (d, 1H, J=7.6 Hz), 7.51 (s, 1H), 7.63 (s, 1H), 8.60 (d, 1H, J=5.1 Hz).

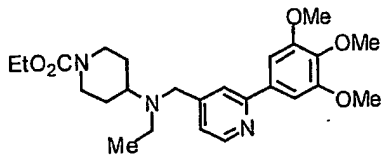
Example 39
Synthesis of 4-[N-methyl-N-[[2-(3,5-dimethoxy-4-hydroxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,5-dimethoxy-4-hydroxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



To an ice-cooled solution of 4-[N-methyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (100 mg) in dichloromethane (5 mL) was added iodotrimethylsilane (173 μL). The mixture was stirred at 0°C for 2 hours and then at room temperature overnight. A small amount of water, ethyl acetate and saturated aqueous sodium hydrogencarbonate were added to the mixture at 0°C and the organic layer was separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and evaporated. The residue was applied to a preparative TLC using chloroform-ammonia saturated methanol (15:1) to give a free base of the title compound which was converted to a tetrahydrochloride by the conventional method.
Yield: 50 mg (52.3%).
^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.68-1.89 (m, 4H), 2.03-2.12 (m, 2H), 2.26 (s, 3H), 2.48-2.60 (m, 1H), 2.98-3.05 (m, 2H), 3.57 (s, 2H), 3.65 (s, 2H), 3.94 (s, 6H), 3.95 (s, 6H), 7.16-7.19 (m, 2H), 7.26 (s, 2H), 7.27 (s, 2H), 7.62-7.68 (m, 2H), 8.56 (d, 1H, J=5.3 Hz), 8.58 (d, 1H, J=5.2 Hz).

Preparation Example 78

Synthesis of 1-(ethoxycarbonyl)-4-[N-ethyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



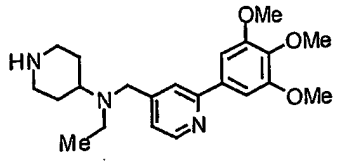
To a solution of 1-(ethoxycarbonyl)-4-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methylamino]piperidine (400 mg) in acetonitrile (5 mL) was added potassium carbonate (13 mg) and iodoethane (145 mg). The mixture was placed in sealed vessel and stirred at 80°C for 2 hours. After removing the solvent in vacuo, ethyl acetate was added, washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The residue was subjected to a column of silica gel using chloroform-methanol (30:1) as an eluent. Fractions containing the product were collected and evaporated to give the title compound as yellow syrup.

Yield: 242 mg (57%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.04 (t, 3H, J=7.1 Hz), 1.25 (t, 3H, J=7.1 Hz), 1.43-1.52 (m, 2H), 1.79 (d, 2H, J=11.5 Hz), 2.60 (q, 2H, J=7.0 Hz), 2.66-2.76 (m, 3H), 3.70 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 4.12 (q, 2H, J=7.0 Hz), 4.20 (br, 2H), 7.23 (s, 2H), 7.26 (d, 1H, J=5.7 Hz), 7.67 (s, 1H), 8.58 (d, 1H, J= 4.9 Hz).

Preparation Example 79

Synthesis of 4-[N-ethyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(ethoxycarbonyl)-4-[N-ethyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (242 mg) was treated in the same manner as described in Preparation Example 77 to give the title compound as yellow syrup.

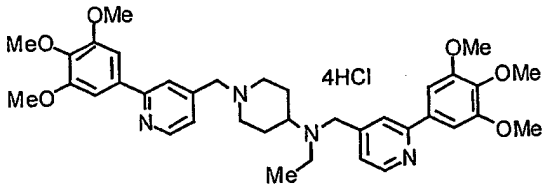
Yield: 150 mg (74%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.03 (t, 3H, J=7.0 Hz), 1.43-1.52 (m, 2H), 1.70 (br, 1H),

1.79 (d, 2H, J=12.3 Hz), 2.53-2.67 (m, 5H), 3.13 (d, 2H, J=11.9 Hz), 3.71 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 7.24 (s, 2H), 7.27 (d, 1H, J=5.1 Hz), 7.68 (s, 1H), 8.57 (d, 1H, J= 4.3 Hz).

Example 40

Synthesis of 4-[N-ethyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



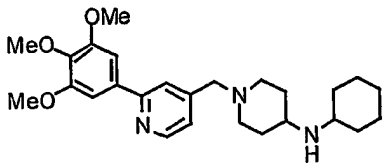
4-[N-ethyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (65 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (50 mg) were condensed in the same manner as described in Example 2. The title compound was obtained after converting a free base to a tetrahydrochloride.

Yield: 121 mg (90%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.03 (t, 3H, J=7.1 Hz), 1.64-1.69 (m, 2H), 1.77 (d, 2H, J=10.7 Hz), 2.01 (t, 2H, J=10.8 Hz), 2.55-2.64 (m, 3H), 2.95 (d, 2H, J=11.1 Hz), 3.53 (s, 2H), 3.71 (s, 2H), 3.90 (s, 6H), 3.97 (s, 12H), 7.20-7.27 (m, 6H), 7.60 (s, 1H), 7.68 (s, 1H), 8.57 (d, 1H, J= 4.9 Hz), 8.59 (d, 1H, J= 5.1 Hz).

Preparation Example 80

Synthesis of 4-(cyclohexylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



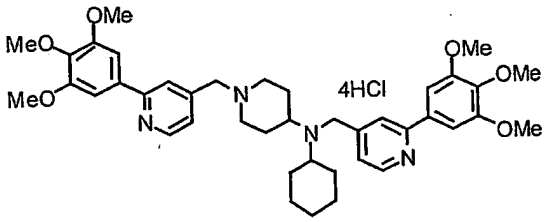
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-pieridone (400 mg) and cyclohexylamine (134 mg) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 342 mg (69%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.05-1.30 (m, 6H), 1.38-1.52 (m, 2H), 1.53-1.80 (m, 3H), 1.87 (br, 4H), 2.07 (t, 2H, J=10.7 Hz), 2.59(br, 2H), 2.86 (br, 2H), 3.54 (s, 2H), 3.90 (s, 3H), 3.97 (s, 6H), 7.19 (d, 1H, J=4.9 Hz), 7.24 (s, 2H), 7.64 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 41

Synthesis of 4-[N-cyclohexyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



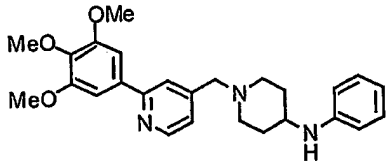
4-(Cyclohexylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (342 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (252 mg) were reacted in the same manner as described in Preparation Example 6. The title compound was obtained after converting the product to a tetrahydrochloride.

Yield: 55 mg (8%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.00-1.39 (m, 6H), 1.58-1.88 (m, 8H), 2.07 (br, 2H), 2.61 (br, 2H), 2.96 (br, 2H), 3.57 (br, 2H), 3.85 (s, 2H), 3.90 (s, 3H), 3.91 (s, 3H), 3.97 (s, 12H), 7.19-7.28 (m, 6H), 7.70 (br, 2H), 8.56 (d, 1H, J=5.1 Hz), 8.60 (d, 1H, J=5.1 Hz).

Preparation Example 81

Synthesis of 4-anilino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



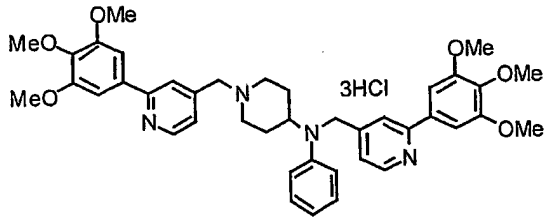
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (1.1 g) and aniline (344 mg) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 1.09 g (81%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.53 (br, 2H), 2.02-2.13 (m, 2H), 2.16-2.32 (m, 2H), 2.86 (br, 2H), 3.32 (br, 1H), 3.59 (s, 2H), 3.88 (s, 3H), 3.95 (s, 6H), 6.57 (d, 2H, J=8.6 Hz), 6.66 (t, 1H, J=7.3 Hz), 7.14 (t, 2H, J=7.9 Hz), 7.20-7.24 (m, 5H), 7.65 (br, 1H), 8.59 (d, 1H, J=5.1 Hz).

Example 42

Synthesis of 4-[N-phenyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



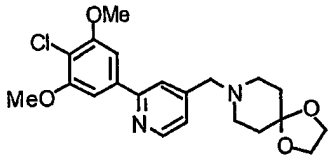
4-Anilino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (1.64 g) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (1.64 g) were reacted in the same manner as described in Preparation Example 9. The title compound was obtained after converting the product to a trihydrochloride.

Yield: 635 mg (20%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.60-2.00 (m, 4H), 2.10-2.35 (m, 2H), 2.99 (br, 2H), 3.58 (br, 3H), 3.86 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 3.94 (s, 6H), 4.52 (s, 2H), 6.66-6.78 (m, 3H), 7.13-7.28 (m, 8H), 7.54 (br, 2H), 8.53 (d, 1H, J=5.1 Hz), 8.58 (d, 1H, J=4.9 Hz).

Preparation Example 82

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone ethylene ketal:



4-Piperidone ethylene ketal (573 mg) and 2-(4-chloro-3,5-dimetoxyphenyl)-4-chloromethylpyridine (1.19 g) were condensed in

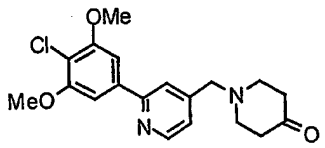
the same manner as described in Example 2 to give the title compound.

Yield: 1.67 g (theoretical amount).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.78 (t, 4H, J=5.6 Hz), 2.58 (br, 4H), 3.61 (s, 2H), 3.67 (s, 4H), 4.02 (s, 6H), 7.25-7.29 (m, 3H), 7.68 (s, 1H), 8.61 (d, 1H, J=4.9 Hz).

Preparation Example 83

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone:



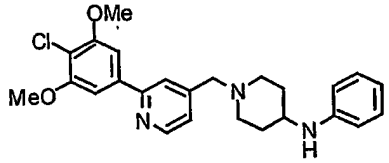
1-[[2-(4-Chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone ethylene ketal (1.67 g) was treated in the same manner as described in Preparation Example 23 to give the title compound.

Yield: 1.29 g (89%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.50 (t, 4H, J=5.8 Hz), 2.81 (t, 4H, J=5.8 Hz), 3.71 (s, 2H), 4.02 (s, 6H), 7.26 (s, 2H), 7.33 (d, 1H, J=4.3 Hz), 7.70 (s, 1H), 8.66 (d, 1H, J=4.9 Hz).

Preparation Example 84

Synthesis of 4-anilino-1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



1-[[2-(4-Chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (600 mg) and aniline (0.18 mL) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

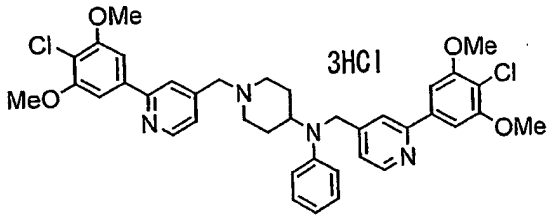
Yield: 465 mg (63%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.49-1.69 (m, 2H), 2.08 (d, 2H, J=7.8 Hz), 2.23 (t, 2H, J=9.3 Hz), 2.87 (d, 2H, J=7.8 Hz), 3.34 (br, 1H), 3.60 (s, 2H), 4.02 (s, 6H), 6.60 (d, 2H, J=7.6 Hz), 6.69 (t, 1H, J=7.3 Hz), 7.10-7.20 (m, 2H), 7.20-7.30 (m, 3H), 7.67 (s, 1H),

8.62 (d, 1H, J=5.2 Hz).

Example 43

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-[N-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-N-phenylamino] piperidine trihydrochloride:



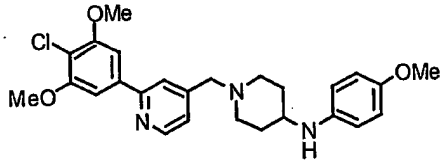
4-Anilino-1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine (230 mg) and 2-(4-chloro-3,5-dimethoxyphenyl)-4-chloromethylpyridine (157 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 104 mg (24%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.70-1.85 (m, 4H), 2.20 (t, 2H, J=2.3 Hz), 3.00 (d, 2H, J=1.3 Hz), 3.59 (s, 2H), 3.96 (s, 6H), 4.00 (s, 6H), 4.56 (s, 2H), 6.65-6.78 (m, 3H), 7.16 (s, 2H), 7.18-7.28 (m, 6H), 7.59 (s, 1H), 7.62 (s,1H), 8.57 (d, 1H, J=5.1 Hz), 8.57 (d, 1H, J=4.8 Hz).

Preparation Example 85

Synthesis of 4-(*p*-anisidino)-1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



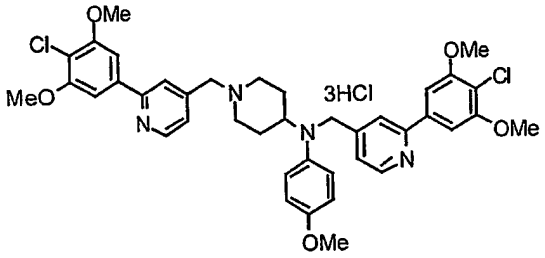
1-[[2-(4-Chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (690 mg) and *p*-anisidine (283 mg) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 646 mg (72%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.45-1.55 (m, 2H), 2.05 (d, 2H, J=11.7 Hz), 2.20 (t, 2H, J=11.2 Hz), 2.87 (d, 2H, J=11.7 Hz), 3.20-3.35 (m, 1H), 3.59 (s, 2H), 3.74 (s, 3H), 4.02 (s, 6H), 6.58 (d, 2H, J=8.7 Hz), 6.77 (d, 2H, J=8.7 Hz), 7.25-7.28 (m, 3H), 7.67 (s, 1H), 8.62 (d, 1H, J=4.9 Hz).

Example 44

Synthesis of 1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]-4-[N-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]- N-(4-methoxyphenyl)amino] piperidine trihydrochloride:



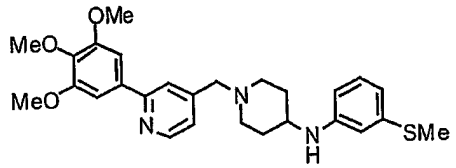
4-(*p*-Anisidino)-1-[[2-(4-chloro-3,5-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine (271 mg) and 2-(4-chloro-3,5-dimethoxyphenyl)-4-chloromethylpyridine (173 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 324 mg (67%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.65-1.90 (m, 4H), 2.16 (t, 2H, J=10.4 Hz), 2.97 (d, 2H, J=7.5 Hz), 3.54-3.60 (m, 1H), 3.58 (s, 2H), 3.73 (s, 3H), 3.97 (s, 6H), 4.00 (s, 6H), 4.46 (s, 2H), 6.74 (d, 2H, J=9.4 Hz), 6.79 (d, 2H, J=9.4 Hz), 7.16 (s, 2H), 7.20-7.29 (m, 4H), 7.59 (s, 1H), 7.62 (s, 1H), 8.56 (d, 1H, J=4.8 Hz), 8.60 (d, 1H, J=4.8 Hz).

Preparation Example 86

Synthesis of 4-(3-methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



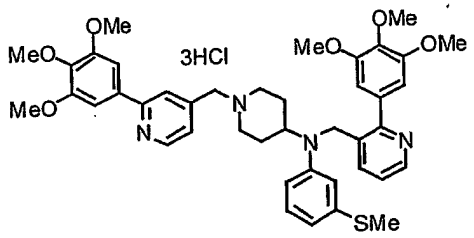
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (1.40 g) and 3-methylthioaniline (655 mg) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 1.01 g (54%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.44-1.60 (m, 2H), 1.98-2.10 (m, 2H), 2.23 (br, 2H), 2.42 (s, 3H), 2.88 (br, 2H), 3.30 (br, 1H), 3.59 (s, 2H), 3.88 (s, 3H), 3.95 (s, 6H), 6.35 (d, 1H, J=7.6 Hz), 6.47 (s, 1H), 6.55 (d, 1H, J=8.6 Hz), 7.05 (t, 1H, J=7.9 Hz), 7.20 (d, 1H, J=4.9 Hz), 7.24 (s, 2H), 7.68 (br, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 45

Synthesis of 4-[N-(3-methylthiophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



4-(3-Methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

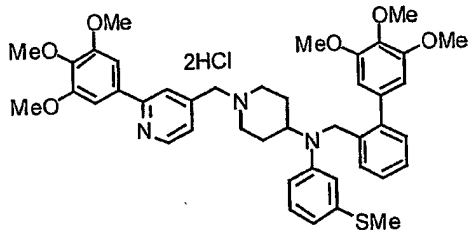
Yield: 45 mg (18%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.58-1.71 (s, 2H), 1.79 (d, 2H, J=10.7 Hz), 2.16 (t, 2H, J=11.2 Hz), 2.38 (s, 3H), 2.96 (d, 2H, J=11.2 Hz), 3.56 (s, 3H), 3.68-3.97 (m, 1H), 3.90 (s, 3H), 3.92 (s, 9H), 3.96 (s, 9H), 4.42 (s, 2H), 6.45 (d, 1H, J=8.3 Hz), 6.52 (s, 1H), 6.61 (d, 1H, J=7.3 Hz), 6.74 (s, 2H), 7.11 (t, 1H, J=8.1 Hz), 7.15-7.26 (m, 4H), 7.54 (s, 1H), 7.68 (d, 1H, J=7.8 Hz), 8.53 (d, 1H, J=3.2 Hz), 8.59 (d,

1H, J=4.8 Hz).

Example 46

Synthesis of 4-[N-(3-methylthiophenyl)-N-[2-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



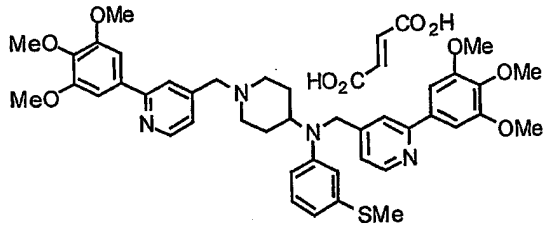
4-(3-Methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 2-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

Yield: 51 mg (23%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.56-1.73 (m, 2H), 1.78-1.87 (m, 2H), 2.10-2.20 (m, 2H), 2.38 (s, 3H), 2.91-2.98 (m, 2H), 3.55 (s, 2H), 3.70-3.80 (m, 1H), 3.88 (s, 6H), 3.90 (s, 3H), 3.92 (s, 3H), 3.96 (s, 6H), 4.35 (s, 2H), 6.47 (d, 1H, J=8.2 Hz), 6.53-6.62 (m, 5H), 7.09 (t, 1H, J=8.0 Hz), 7.18-7.40 (m, 6H), 7.54 (s, 1H), 8.58 (d, 1H, J=4.7 Hz).

Example 47

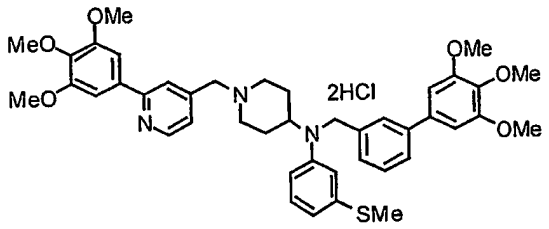
Synthesis of 4-[N-(3-methylthiophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine fumarate:



4-(3-Methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title

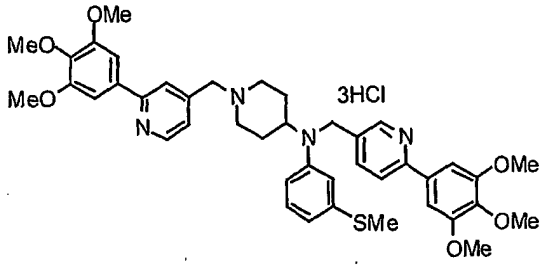
compound was obtained as white powder after converting a free base to a fumarate.
Yield: 14 mg (5%).
^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.76-1.86 (m, 5H), 2.17-2.23 (m, 2H), 2.39 (s, 3H), 2.97-3.00 (m, 2H), 3.58 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.54 (s, 2H), 6.47-6.50 (m, 1H), 6.63 (s, 1H), 6.64 (s, 1H), 7.10-7.15 (m, 2H), 7.15 (s, 2H), 7.20-7.21 (m, 1H), 7.22 (s, 2H), 7.55 (s, 1H), 7.59 (s, 1H), 8.56 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=5.1 Hz).

Example 48
Synthesis of 4-[N-(3-methylthiophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



4-(3-Methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.
Yield: 60 mg (24%).
^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.65-1.91 (m, 4H), 2.18 (t, 2H, J=10.5 Hz), 2.38 (s, 3H), 2.97 (d, 2H, J=10.9 Hz), 3.58 (s, 2H), 3.70-3.85 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.56 (s, 2H), 6.52 (d, 1H, J=8.4 Hz), 6.59 (d, 1H, J=7.6 Hz), 6.65 (s, 1H), 6.72 (s, 2H), 7.10 (t, 2H, J=8.0 Hz), 7.19-7.25 (m, 4H), 7.31-7.42 (m, 3H), 7.60 (s, 1H), 8.59 (d, 1H, J=7.8 Hz).

Example 49
Synthesis of 4-[N-(3-methylthiophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



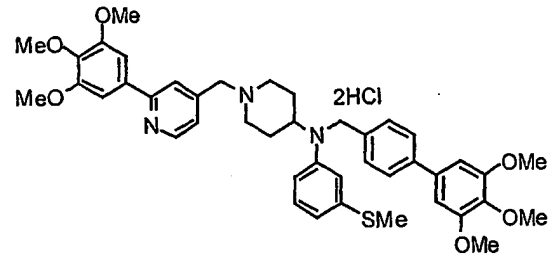
4-(3-Methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 22 mg (9%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.50-2.05 (m, 4H), 2.20 (br, 2H), 2.37 (s, 3H), 3.05 (br, 2H), 3.50-3.70 (br, 3H), 3.86 (s, 3H), 3.87 (s, 3H), 3.92 (s, 6H), 3.95 (s, 6H), 4.52 (s, 2H), 6.49 (d, 1H, J=8.3 Hz), 6.62 (br, 2H), 7.09 (t, 1H, J=8.2 Hz), 7.18-7.30 (m, 6H), 7.58 (s, 2H), 8.54 (br, 1H), 8.60 (br, 1H).

Example 50

Synthesis of 4-[N-(3-methylthiophenyl)-N-[4-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



4-(3-Methylthioanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 4-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

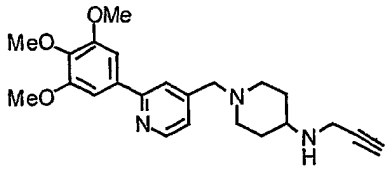
Yield: 57 mg (22%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.58-1.83 (m, 4H), 2.20 (t, 2H, J=11.3 Hz), 2.39 (s, 3H), 2.98 (d, 2H, J=11.1 Hz), 3.58 (s, 2H), 3.88 (s, 3H), 3.90 (s,

3H), 3.91 (s, 6H), 3.96 (s, 6H), 4.53 (s, 2H), 6.51 (dd, 1H, J=8.4 Hz, 2.4 Hz), 6.60 (d, 1H, J=8.0 Hz), 6.64 (s, 1H), 6.75 (s, 2H), 7.10 (t, 1H, J=8.1 Hz), 7.24-7.33 (m, 4H), 7.47 (d, 2H, J=8.0 Hz), 7.61 (s, 1H), 8.59 (d, 1H, J=5.0 Hz).

Preparation Example 87

Synthesis of 4-propargylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



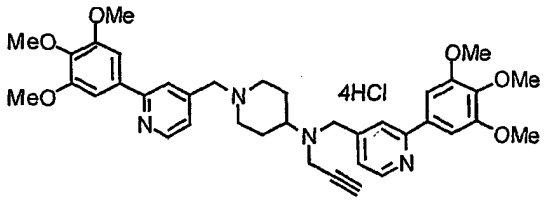
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (400 mg) and propargylamine (80 mg) were reacted in the same manner as described in Preparation Example 25 to give the title compound.

Yield: 227 mg (63%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.38-1.51 (m, 2H), 1.83-1.86 (m, 3H), 2.10-2.15 (m, 2H), 2.21 (s, 1H), 2.74 (br, 1H), 2.83-2.87 (m, 2H), 3.45 (s, 2H), 3.56 (s, 2H), 3.89 (s, 3H), 3.96 (s, 6H), 7.19 (d, 1H, J=4.9 Hz), 7.24 (s, 2H), 7.65 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 51

Synthesis of 4-[N-propargyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine tetrahydrochloride:



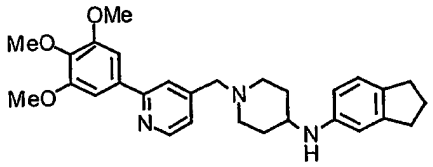
4-Propargylamino-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (227 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (226 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a tetrahydrochloride.

Yield: 128 mg (23%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.48-2.40 (m, 7H), 2.72 (br, 1H), 3.02 (br, 2H), 3.39 (s, 2H), 3.64 (br, 2H), 3.84 (s, 2H), 3.91 (s, 6H), 3.98 (s, 6H), 3.99 (s, 6H), 7.22-7.29 (m, 6H), 7.66 (br, 2H), 8.60 (d, 1H, J=4.9 Hz), 8.62 (d, 1H, J=4.9 Hz).

Preparation Example 88

Synthesis of 4-(5-indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



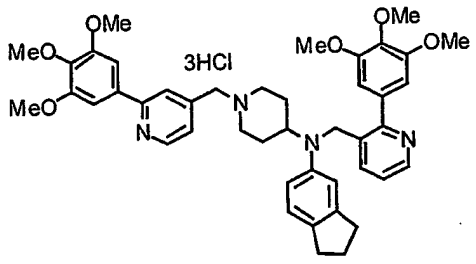
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (1.40 g) and 5-aminoindan (680 mg) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 1.22 g (59%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 1.40-1.57 (m, 2H), 2.00-2.15 (m, 5H), 2.19-2.25 (m, 2H), 2.77-2.93 (m, 6H), 3.30 (br, 1H), 3.58 (s, 2H), 3.91 (s, 3H), 3.97 (s, 6H), 6.41 (d, 1H, J=8.0 Hz), 6.52 (s, 1H), 7.01 (d, 1H, J=8.0 Hz), 7.21-7.26 (m, 3H), 7.64 (s, 1H), 8.60 (d, 1H, J=4.9 Hz).

Example 52

Synthesis of 4-[N-(indan-5-yl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



4-(5-Indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (142 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title

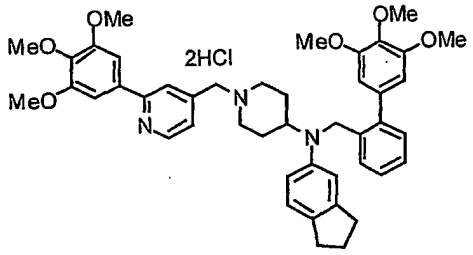
compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 90 mg (41%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.54-1.67 (m, 2H), 1.74-1.83 (m, 2H), 1.98-2.07 (m, 2H), 2.09-2.98 (m, 2H), 3.55 (s, 2H), 3.64-3.74 (m, 1H), 3.90 (s, 3H), 3.91 (s, 6H), 3.92 (s, 3H), 3.96 (s, 6H), 4.41 (s, 2H), 6.49 (dd, 1H, J=8.2 Hz, 2.4 Hz), 6.59 (s, 1H), 6.74 (s, 2H), 7.04 (d, 1H, J=8.2 Hz), 7.15-7.20 (m, 2H), 7.22 (s, 2H), 7.54 (s, 1H), 7.77 (dd, 1H, J=7.8 Hz, 1.4 Hz), 8.52 (dd, 1H, J=4.7 Hz, 1.8 Hz), 8.59 (d, 1H, J=5.1 Hz).

Example 53

Synthesis of 4-[N-(indan-5-yl)-N-[2-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



4-(5-Indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (142 mg) and 2-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

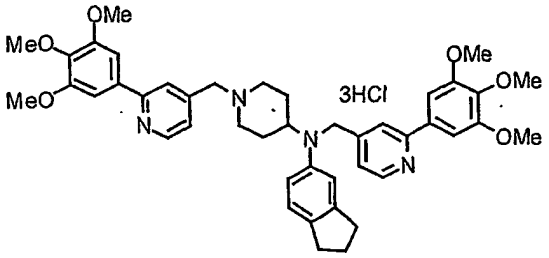
Yield: 115 mg (47%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.56-1.66 (m, 2H), 1.80-1.83 (m, 2H), 2.00-2.05 (m, 2H), 2.11-2.18 (m, 2H), 2.77-2.83 (m, 4H), 2.92-2.95 (m, 2H), 3.55 (s, 2H), 3.72 (br, 1H), 3.87 (s, 6H), 3.90 (s, 3H), 3.92 (s, 3H), 3.96 (s, 6H), 4.34 (s, 2H), 6.49 (d, 1H, J=8.3 Hz), 6.56 (s, 2H), 6.60 (s, 1H), 7.02 (d, 1H, J=8.3 Hz), 7.17-7.27 (m, 5H), 7.42-7.45 (m, 1H), 7.54 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 54

Synthesis of 4-[N-(indan-5-yl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine

trihydrochloride:



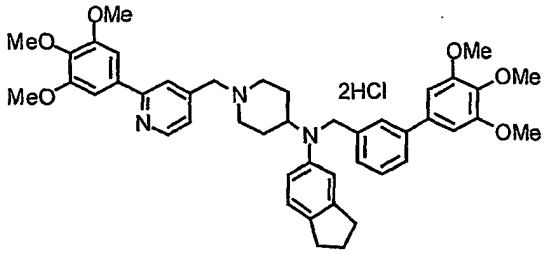
4-(5-Indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (142 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as white powder after converting a free base to a trihydrochloride.

Yield: 23 mg (9%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.60-1.95 (m, 4H), 2.00 (quint, 2H, J=7.3 Hz), 2.20 (br, 2H), 2.75-2.81 (m, 4H), 2.99 (br, 2H), 3.58 (br, 2H), 3.77 (s, 1H), 3.86 (s, 3H), 3.87 (s, 3H), 3.91 (s, 6H), 3.94 (s, 6H), 4.49 (s, 2H), 6.51 (d, 1H, J=8.3 Hz), 6.62 (s, 1H), 7.02 (d, 1H, J=8.0 Hz), 7.16 (s, 2H), 7.18-7.22 (m, 4H), 7.57 (br, 2H), 8.52 (d, 1H, J=4.9 Hz), 8.57 (d, 1H, J=4.9 Hz).

Example 55

Synthesis of 4-[N-(indan-5-yl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



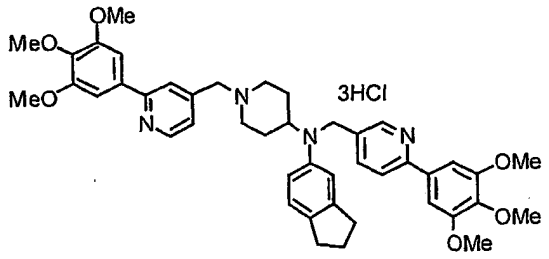
4-(5-Indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (60 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

Yield: 18 mg (19%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.60-1.95 (m, 4H), 2.00 (quint, 2H, J=7.2 Hz), 2.20 (br, 2H), 2.75-2.81 (m, 4H), 2.95 (br, 2H), 3.60 (br, 2H), 3.85 (br, 1H), 3.86 (s, 3H), 3.87 (s, 6H), 3.88 (s, 3H), 3.94 (s, 6H), 4.51 (s, 2H), 6.54 (d, 1H, J=8.2 Hz), 6.66 (s, 1H), 6.70 (s, 2H), 7.01 (d, 1H, J=8.4 Hz), 7.19 (d, 1H, J=4.9 Hz), 7.19-7.42 (m, 6H), 7.60 (br, 1H), 8.59 (br, 1H).

Example 56

Synthesis of 4-[N-(indan-5-yl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]piperidine trihydrochloride:



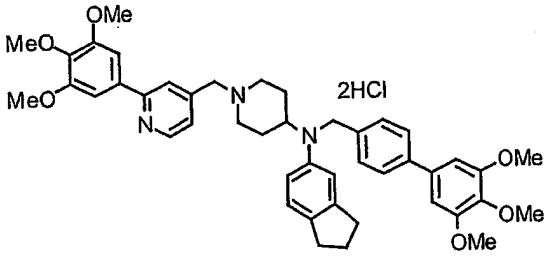
4-(5-Indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 138 mg (63%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.71-1.91 (m, 4H), 1.98-2.06 (m, 2H), 2.13-2.22 (m, 2H), 2.76-2.84 (m, 4H), 2.94-3.05 (m, 2H), 3.57 (s, 2H), 3.69-3.78 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 6H), 3.96 (s, 6H), 4.50 (s, 2H), 6.57 (dd, 1H, J=8.2 Hz, 2.3 Hz), 6.67 (s, 1H), 7.04 (d, 1H, J=8.4 Hz), 7.20-7.22 (m, 1H), 7.22 (s, 2H), 7.23 (s, 2H), 7.57-7.62 (m, 1H), 7.60 (s, 1H), 7.65 (dd, 1H, J=8.2 Hz, 2.2 Hz), 8.58-8.62 (m, 2H).

Example 57

Synthesis of 4-[N-(indan-5-yl)-N-[4-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



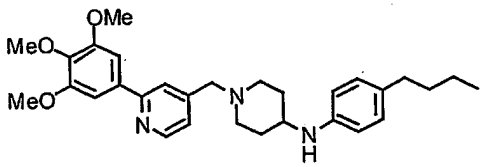
4-(5-Indanylamino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (143 mg) and 4-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

Yield: 95 mg (39%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.74-1.90 (m, 4H), 2.01-2.06 (m, 2H), 2.16-2.22 (m, 2H), 2.78-2.84 (m, 4H), 2.96-2.99 (m, 2H), 3.58 (s, 2H), 3.72 (br, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.96 (s, 6H), 4.51 (s, 2H), 6.55 (d, 1H, J=8.3 Hz), 6.67 (s, 1H), 6.72 (s, 2H), 7.04 (d, 1H, J=8.3 Hz), 7.20 (d, 1H, J=5.1 Hz), 7.23 (s, 2H), 7.35 (d, 2H, J=8.1 Hz), 7.47 (d, 2H, J=8.1 Hz), 7.61 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 89

Synthesis of 4-(4-butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine:



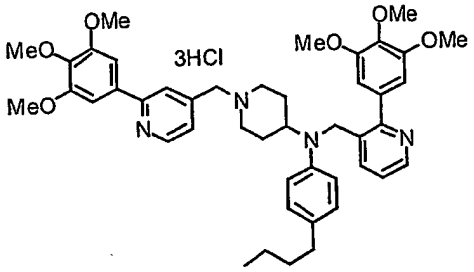
1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]-4-piperidone (1.24 g) and 4-butylaniline (149 mg) were reacted in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 1.23 g (72%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 0.82 (t, 3H, J=7.3 Hz), 1.20-1.30 (m, 2H), 1.38-1.50 (m, 4H), 1.92-2.25 (m, 4H), 2.40 (t, 2H, J=7.7 Hz), 2.77 (br, 2H), 3.21 (br, 1H), 3.50 (s, 2H), 3.82 (s, 3H), 3.89 (s, 6H), 6.45 (d, 2H, J=7.8 Hz), 6.89 (d, 2H, J=8.0 Hz), 7.13 (d, 1H, J=4.9 Hz), 7.18 (s, 2H), 7.58 (s, 1H), 8.52 (d, 1H, J=4.9 Hz).

Example 58

Synthesis of 4-[N-(4-butylphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-3-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



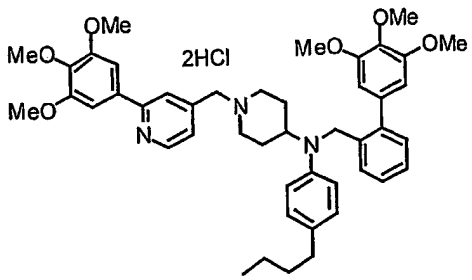
4-(4-Butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (147 mg) and 3-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 58 mg (27%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 0.91 (t, 3H, J=7.3 Hz), 1.32-1.35 (m, 2H), 1.50-1.70 (m, 4H), 1.75 (br, 2H), 2.10-2.20 (m, 2H), 2.49 (t, 2H, J=7.6 Hz), 2.95 (br, 2H), 3.55 (s, 2H), 3.70 (br, 1H), 3.90 (s, 3H), 3.91 (s, 6H), 3.92 (s, 3H), 3.96 (s, 6H), 4.41 (s, 2H), 6.59 (d, 2H, J=8.8 Hz), 6.74 (s, 2H), 7.00 (d, 2H, J=8.6 Hz), 7.16-7.17 (m, 1H), 7.19 (d, 1H, J=4.9 Hz), 7.22 (s, 2H), 7.54 (s, 1H), 8.59 (d, 1H, J=7.5 Hz), 8.52 (br, 1H), 8.59 (d, 1H, J=4.9 Hz).

Example 59

Synthesis of 4-[N-(4-butylphenyl)-N-[2-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



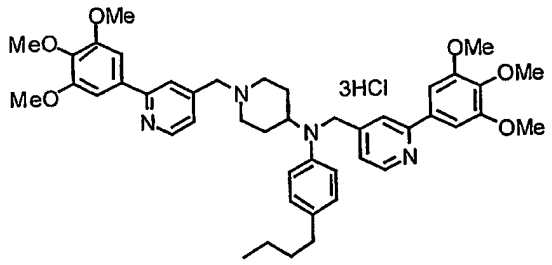
4-(4-Butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (147 mg) and 2-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

Yield: 59 mg (24%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 0.90 (t, 3H, J=7.4 Hz), 1.25-1.41 (m, 2H), 1.48-1.75 (m, 4H), 1.81 (d, 2H, J=11.7 Hz), 2.13 (t, 2H, J=11.2 Hz), 2.48 (t, 2H, J=7.5 Hz), 2.93 (d, 2H, J=11.2 Hz), 3.55 (s, 2H), 3.65-3.80 (m, 1H), 3.87 (s, 6H), 3.90 (s, 3H), 3.92 (s, 1H), 3.96 (s, 6H), 4.33 (s, 2H), 6.56 (s, 2H), 6.60 (d, 2H, J=8.5 Hz), 6.98 (d, 2H, J=8.5 Hz), 7.18 (d, 1H, J=4.9 Hz), 7.21 (s, 2H), 7.20-7.37 (m, 3H), 7.41 (br, 1H), 7.54 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).

Example 60

Synthesis of 4-[N-(4-buthylphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



4-(4-Butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (196 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (129 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as white powder after converting a free base to a trihydrochloride.

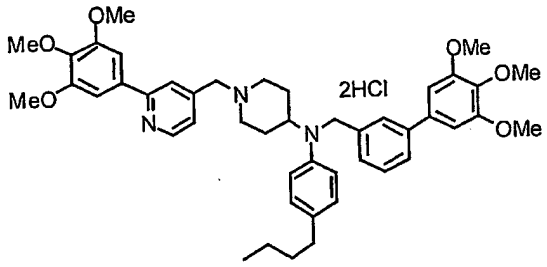
Yield: 20 mg (6%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 0.88 (t, 3H, J=7.3 Hz), 1.20-1.35 (m, 2H), 1.49-1.60 (m, 2H), 1.62-2.02 (m, 4H), 2.20 (br, 2H), 2.46 (t, 2H, J=7.3 Hz), 3.05 (br, 2H), 3.60 (br, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 3.94 (s, 6H), 4.49 (s, 2H), 6.62 (d, 2H, J=8.3 Hz), 6.98 (d, 2H, J=8.3 Hz), 7.13 (s, 2H), 7.15-7.40 (m, 4H), 7.55 (br, 2H), 8.52 (d, 1H, J=4.9 Hz), 8.60 (br, 1H).

Example 61

Synthesis of

4-[N-(4-butylphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimeth oxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



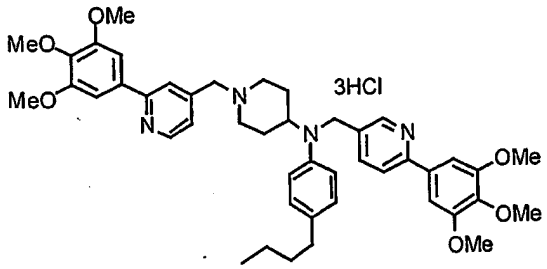
4-(4-Butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (147 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

Yield: 102 mg (42%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 0.90 (t, 3H, J=7.4 Hz), 1.30-1.36 (m, 2H), 1.48-1.56 (m, 2H), 1.76-1.89 (m, 4H), 2.19 (br, 2H), 2.48 (t, 2H, J=7.8 Hz), 2.97 (br, 2H), 3.58 (s, 2H), 3.86 (br, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 3.95 (s, 6H), 4.54 (s, 2H), 6.68 (d, 2H, J=8.6 Hz), 6.72 (s, 2H), 7.00 (d, 2H, J=8.6 Hz), 7.20-7.27 (m, 2H), 7.23 (s, 2H), 7.32-7.40 (m, 2H), 7.44 (s, 1H), 7.62 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Example 62

Synthesis of 4-[N-(4-butylphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



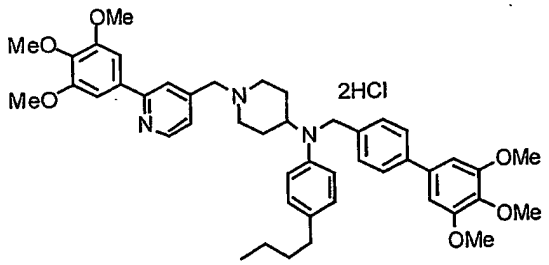
4-(4-Butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (147 mg) and 5-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a trihydrochloride.

Yield: 65 mg (21%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 0.90 (t, 3H, J=7.3 Hz), 1.32-1.36 (m, 2H), 1.50-1.54 (m, 2H), 1.70-1.95 (m, 4H), 2.17 (br, 2H), 2.49 (t, 2H, J=7.7 Hz), 2.96 (br, 2H), 3.58 (s, 2H), 3.75 (br, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 6H), 3.96 (s, 6H), 4.50 (s, 2H), 6.68 (d, 2H, J=8.6 Hz), 7.00 (d, 2H, J=8.6 Hz), 7.20-7.22 (m, 3H), 7.23 (s, 2H), 7.58-7.66 (m, 3H), 8.59 (br, 1H), 8.60 (br, 1H).

Example 63

Synthesis of 4-[N-(4-butylphenyl)-N-[4-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



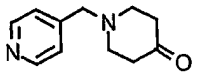
4-(4-Butylanilino)-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine (147 mg) and 4-(3,4,5-trimethoxyphenyl)benzyl chloride (114 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as yellow powder after converting a free base to a dihydrochloride.

Yield: 82 mg (33%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 0.90 (t, 3H, J=7.3 Hz), 1.30-1.36 (m, 2H), 1.51-1.55 (m, 2H), 1.79-1.90 (m, 4H), 2.18 (br, 2H), 2.48 (t, 2H, J=7.7 Hz), 2.98 (d, 2H, J=10.7 Hz), 3.57 (s, 2H), 3.72-3.85 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.96 (s, 6H), 4.50 (s, 2H), 6.66 (d, 2H, J=8.8 Hz), 6.75 (s, 2H), 7.00 (d, 2H, J=8.8 Hz), 7.20 (d, 1H, J=4.9 Hz), 7.22 (s, 2H), 7.33 (d, 2H, J=8.2 Hz), 7.47 (d, 2H, J=8.2 Hz), 7.61 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

Preparation Example 90

Synthesis of 1-(4-pycolyl)-4-piperidone:



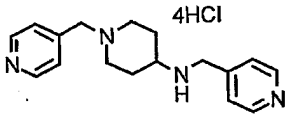
4-piperidone hydrochloride monohydrate (922 mg) and 4-picolyl chloride hydrochloride (820 mg) were reacted in the same manner as described in Example 9 to give the title compound.

Yield: 870 mg (92%).

^{1}H-NMR (400 MHz, $CDCl_3$)δ: 2.46 (t, 4H, J=5.9 Hz), 2.74 (t, 4H, J=6.2 Hz), 3.61 (s, 2H), 7.29 (d, 2H, J=6.2 Hz), 8.55 (dd, 2H, J=6.2 Hz, 1.1 Hz).

Preparation Example 91

Synthesis of 1-(4-pycolyl)-4-(4-pycolylamino)piperidine tetrahydrochloride:



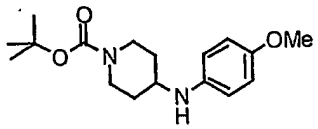
1-(4-pycolyl)-4-piperidone (870 mg) and 4-picolylamine (497 mg) were coupled in the same manner as described in Preparation Example 37. The title compound was obtained as pale brown powder after converting a free base to tetrahydrochloride.

Yield: 363 mg (19%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$)δ: 1.37-1.51 (m, 2H), 1.82-1.90 (m, 2H), 2.04 (dt, 2H, J=11.6 Hz, 2.7 Hz), 2.44-2.55 (m, 1H), 2.76-2.82 (m, 2H), 3.47 (s, 2H), 3.82 (s, 2H), 7.23-7.26 (m, 4H), 8.50-8.53 (m, 4H).

Preparation Example 92

Synthesis of 4-(*p*-anisidino)-1-(tert-butoxycarbonyl)piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (116 g) and *p*-anisidine (68.3 g) were condensed in the same manner as described in Preparation Example 37 to give the title compound.

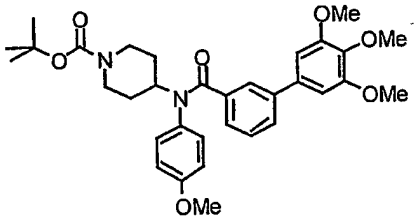
Yield: 125 g (74%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23-1.35 (m, 2H), 1.46 (s, 9H), 1.96-2.06 (m, 2H), 2.83-2.96 (m, 2H), 3.27-3.38 (m, 1H), 3.74 (s, 9H), 3.94-4.12 (m, 2H), 6.58 (d, 2H, J=9.0 Hz), 6.77 (d, 2H, J=9.0 Hz).

Preparation Example 93

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzoylamino]piperidine:



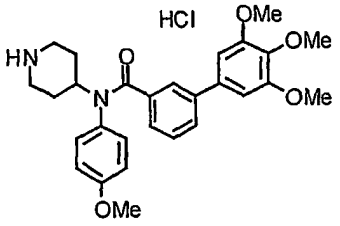
4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 3-(3,4,5-trimethoxyphenyl)benzoic acid (577 mg) were condensed in the same manner as described in Example 1 to give the title compound.

Yield: 416 mg (36%).

Preparation Example 94

Synthesis of

4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzoylamino]piperidine hydrochloride:

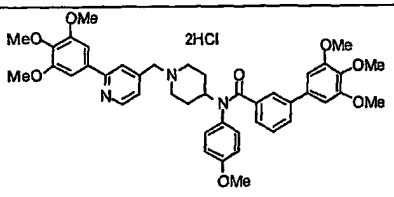
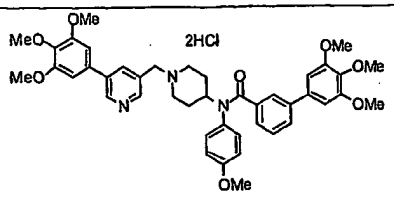


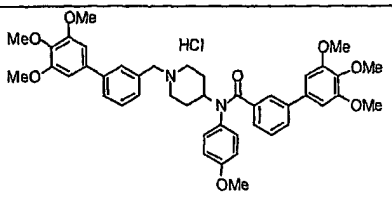
To a solution of 1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzoylamino]piperidine (416 mg) in ethyl acetate (5 mL) was added 4 M hydrogen chloride in ethyl acetate (5 mL). The mixture was stirred at room temperature for 4 hr, resulting precipitates were collected and washed with ethyl acetate on a funnel to give the title compound.

Yield: 315 mg (85%)

Examples 64 to 66

These compounds were prepared by the condensation of 4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzoylamino]]piperidine hydrochloride with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

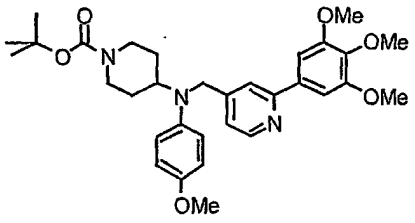
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
64		68%	1.53-1.55 (m, 2H), 1.89 (d, 2H, J=12.0 Hz), 2.23 (t, 2H, J=12.0 Hz), 2.91 (d, 2H, J=11.0 Hz), 3.51 (s, 2H), 3.70 (s, 3H), 3.84 (s, 3H), 3.87 (s, 9H), 3.92 (s, 6H), 4.78 (br, 1H), 6.54 (s, 2H), 6.72 (d, 2H, J=8.5 Hz), 6.94 (d, 2H, J=8.5 Hz), 7.13-7.20 (m, 4H), 7.18 (s, 2H), 7.32 (d, 1H, J=5.3 Hz), 7.45 (s, 1H), 8.19 (d, 1H, J=4.9 Hz).
65		52%	1.66-1.89 (m, 4H), 2.05-2.17 (m, 2H), 2.97 (d, 2H, J=10.3 Hz), 3.43-3.60 (m, 1H), 3.57 (s, 2H), 3.86 (s, 3H), 3.87 (s, 6H), 3.91 (s, 6H), 4.42 (s, 2H), 6.63 (s, 2H), 6.72-6.79 (m, 6H), 7.64 (s, 1H),

			7.78 (br, 1H), 8.46 (d, 2H, J=1.6 Hz), 8.59 (d, 1H, J=2.4 Hz), 8.68 (d, 1H, J=2.2 Hz).
66		75%	1.42-1.58 (m, 2H), 1.85-1.92 (m, 2H), 2.14-2.23 (m, 2H), 2.93-3.03 (m, 2H), 3.56 (s, 2H), 3.70 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.87 (s, 6H), 3.90 (s, 6H), 4.79 (br, 1H), 6.54 (s, 2H), 6.70 (d, 2H, J=8.9 Hz), 6.74 (s, 2H), 6.93 (d, 2H, J=8.9 Hz), 7.17-7.23 (m, 3H), 7.31-7.43 (m, 5H).

Preparation Example 95

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (2.21 g) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (2.12 g) were condensed in the same manner as described in Example 9 to give the title compound.

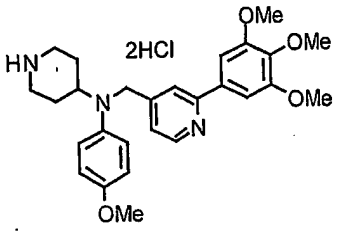
Yield: 3.76 g (93%)

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40-1.64 (m, 2H), 1.44 (s, 9H), 1.82-1.91 (m, 2H), 2.71-2.84 (m, 2H), 3.62-3.73 (m, 1H), 3.74 (s, 3H), 3.89 (s, 3H), 3.94 (s, 6H), 4.10-4.30 (m, 2H), 4.40 (s, 2H), 6.76 (d, 2H, J=9.4 Hz), 6.79 (d, 2H, J=9.8 Hz), 7.14-7.19 (m, 3H), 7.56 (s, 1H), 8.55 (d, 1H, J=5.1 Hz).

Preparation Example 96

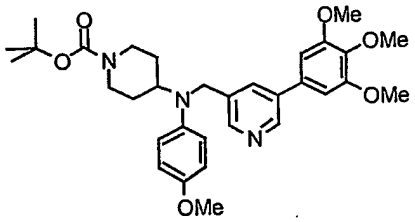
Synthesis of

4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



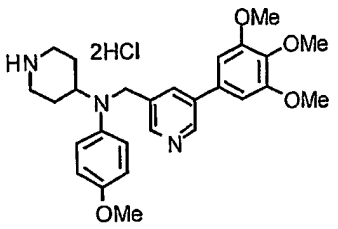
1-(tert-Butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (3.76 g) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 3.77 g (theoretical yield).

Preparation Example 97
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine :



4-(*p*-anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Preparation Example 9 to give pale yellow amorphous of the title compound.
Yield: 159 mg (14%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.50-1.65 (m, 2H), 1.83-1.91 (m, 2H), 2.70-2.84 (m, 2H), 3.53-3.62 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.91 (s, 6H), 4.10-4.29 (m, 2H), 4.41 (s, 2H), 6.66 (s, 2H), 6.76-6.84 (m, 4H), 7.70 (s, 1H), 8.49 (s, 1H), 8.63 (d, 1H, J=2.1 Hz).

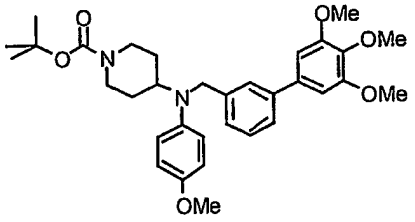
Preparation Example 98
Synthesis of
4-[N-(4-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (159 mg) was treated in the same manner as described in Preparation Example 94 to give pale yellow powder of the title compound.
Yield: 142 mg (94%).

Preparation Example 99

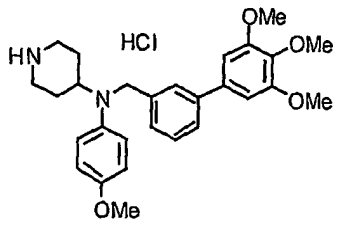
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine :



4-(p-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give pale yellow amorphous of the title compound.
Yield: 1.12 g (90%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.50-1.63 (m, 2H), 1.82-1.91 (m, 2H), 2.71-2.83 (m, 2H), 3.69 (tt, 1H, J=11.5 Hz, 3.5 Hz), 3.73 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 4.10-4.28 (m, 2H), 4.42 (s, 2H), 6.71 (s, 2H), 6.78 (s, 4H), 7.24-7.28 (m, 1H), 7.31-7.40 (m, 2H), 7.42 (s, 1H).

Preparation Example 100

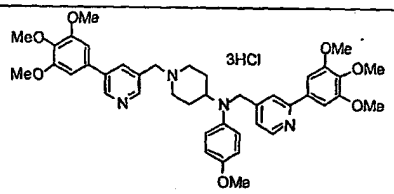
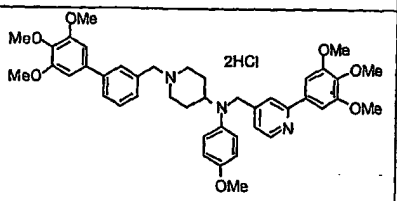
Synthesis of
4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

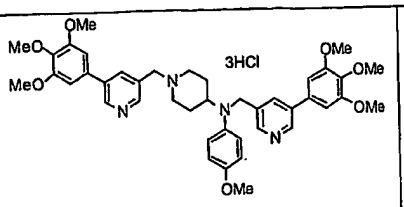
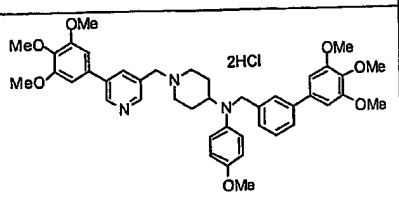
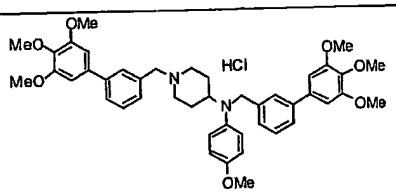


1-(tert-Butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (1.12 g) was treated in the same manner as described in Preparation Example 94 to give pale yellow powder of the title compound.
Yield: 980 mg (99%).

Examples 67 to 71.

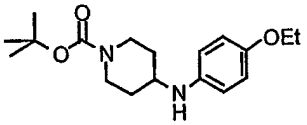
These compounds were obtained by the condensation of amines obtained in Preparation Examples 96, 98 and 100 with chloride derivatives obtained in Preparation Examples 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
67		62%	1.60-1.92 (m, 4H), 2.08-2.22 (m, 2H), 2.92-3.06 (m, 2H), 3.54-3.64 (m, 3H), 3.73 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 12H), 4.43 (s, 2H), 6.70-6.81 (m, 6H), 7.12-7.17 (m, 3H), 7.56 (s, 1H), 7.76 (s, 1H), 8.49 (d, 1H, J=1.8 Hz), 8.53 (d, 1H, J=5.1 Hz), 8.70 (s, 1H).
68		54%	1.65-1.79 (m, 2H), 1.81-1.90 (m, 2H), 2.04-2.18 (m, 2H), 2.94-3.06 (m, 2H), 3.52-3.66 (m, 3H), 3.72 (s, 3H), 3.89 (s, 6H), 3.92 (s, 6H), 3.93 (s, 6H), 4.44 (s, 2H), 6.70-6.80 (m, 6H), 7.13-7.17 (m, 3H), 7.24-7.50 (m, 4H), 7.55 (s, 1H), 8.53 (d, 1H, J=4.9 Hz).

69		52%	1.66-1.89 (m, 4H), 2.05-2.17 (m, 2H), 2.97 (d, 2H, J=10.3 Hz), 3.43-3.60 (m, 1H), 3.57 (s, 2H), 3.86 (s, 3H), 3.87 (s, 6H), 3.91(s, 6H), 4.42 (s, 2H), 6.63 (s, 2H), 6.72-6.79 (m, 6H), 7.64 (s, 1H), 7.78 (br, 1H), 8.46 (d, 2H, J=1.6 Hz), 8.59 (d, 1H, J=2.4 Hz), 8.68 (d, 1H, J=2.2 Hz).
70		69%	1.55-1.97 (m, 4H), 2.06-2.21 (m, 2H), 2.92-3.07 (m, 2H), 3.53-3.68 (m, 3H), 3.72 (s, 3H), 3.87 (s, 3H), 3.89 (s, 6H), 3.94 (s, 3H), 4.46 (s, 2H), 6.69 (s, 2H), 6.73-6.82 (m, 6H), 7.22-7.29 (m, 1H), 7.32 (t, 1H, J=7.4 Hz), 7.36 (d, 1H, J=7.8 Hz), 7.41 (s, 1H), 7.79(br, 1H), 8.48 (s, 1H), 8.71(br, 1H).
71		75%	1.69-1.89 (m, 4H), 2.06-2.15 (m, 2H), 2.96-3.04 (m, 2H), 3.56-3.66 (m, 1H), 3.57 (s, 2H), 3.72 (s, 3H), 3.87 (s, 3H), 3.89 (s, 9H), 3.92 (s, 6H), 4.46 (s, 2H), 6.70 (s, 2H), 6.71-6.79 (m, 6H), 7.23-7.47 (m, 8H).

Preparation Example 101

Synthesis of 1-(tert-butoxycarbonyl)-4-(4-ethoxyphenylamino)piperidine:



1-(tert-butoxycarbonyl)-4-piperidinone (5.00 g) and *p*-phenetidine (3.28 g) was treated in the same manner as described in Preparation Example 37 to give brown powder of the title compound.

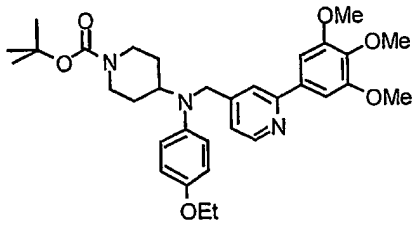
Yield: 7.00 g (91%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21-1.31 (m, 2H), 1.37 (t, 3H, J=7.0 Hz), 1.46 (s, 9H), 1.97-2.05 (m, 2H), 2.84-2.95 (m, 2H), 3.28-3.37 (m, 1H), 3.96 (q, 2H, J=7.0 Hz), 3.99-4.10 (m, 2H), 6.57 (d, 2H, J=8.8 Hz), 6.77 (d, 2H, J=9.0 Hz).

Preparation Example 102

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-ethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-ethoxyphenyl)amino]piperidine (641 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

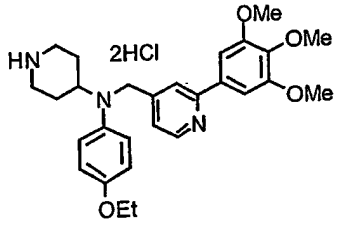
Yield: 1.08 g (94%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, 3H, J=7.9 Hz), 1.44 (s, 9H), 1.49-1.58 (m, 2H), 1.82-1.92 (m, 2H), 2.70-2.85 (m, 2H), 3.62-3.72 (m, 1H), 3.89 (s, 3H), 3.94 (s, 6H), 4.12-4.29 (m, 2H), 4.39 (s, 2H), 6.75 (d, 2H, J=9.2 Hz), 6.78 (d, 2H, J=9.6 Hz), 7.14-7.18 (m, 3H), 7.55 (s, 1H), 8.54 (d, 1H, J=5.1 Hz).

Preparation Example 103

Synthesis of

4-[N-(4-ethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



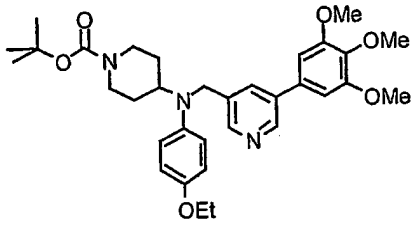
1-(tert-Butoxycarbonyl)-4-[N-(4-ethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (1.08 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 1.01 g (98%).

Preparation Example 104

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-ethoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-ethoxyphenyl)amino]piperidine (641 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

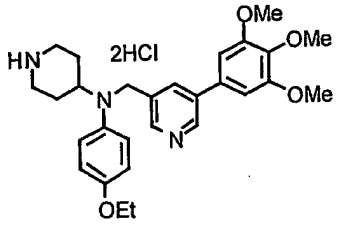
Yield: 452 mg (39%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, 3H, J=6.8 Hz), 1.44 (s, 9H), 1.50-1.60 (m, 2H), 1.82-1.90 (m, 1H), 2.68-2.82 (m, 2H), 3.52-3.61 (m, 1H), 3.88 (s, 3H), 3.90 (s, 6H), 3.94 (q, 2H, J=7.0 Hz), 4.10-4.25 (m, 2H), 4.40 (s, 2H), 6.66 (s, 2H), 6.77 (d, 2H, J=9.2 Hz), 6.81 (d, 2H, J=9.2 Hz), 7.67 (s, 1H), 8.49 (d, 1H, J=2.0 Hz), 8.62 (d, 1H, J=2.1 Hz).

Preparation Example 105

Synthesis of

4-[N-(4-ethoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



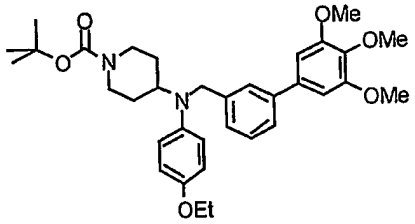
1-(tert-Butoxycarbonyl)-4-[N-(4-ethoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (452 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 380 mg (88%).

Preparation Example 106

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-ethoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-ethoxyphenyl)amino]piperidine (641 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

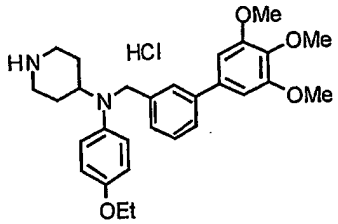
Yield: 1.06 g (92%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (t, 3H, J=7.0 Hz), 1.44 (s, 9H), 1.53-1.59 (m, 2H), 1.83-1.91 (m, 2H), 2.70-2.83 (m, 2H), 3.64-3.73 (m, 1H), 3.88 (s, 3H), 3.90 (s, 6H), 3.94 (q, 2H, J=7.0 Hz), 4.10-4.29 (m, 2H), 4.41 (s, 2H), 6.71 (s, 2H), 6.76 (s, 4H), 7.26 (d, 1H, J=7.9 Hz), 7.33 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.38 (d, 1H, J=7.6 Hz), 7.42 (s, 1H).

Preparation Example 107

Synthesis of

4-[N-(4-ethoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

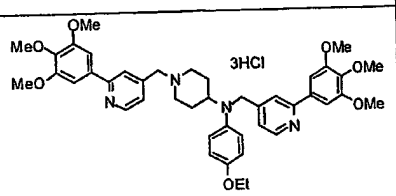
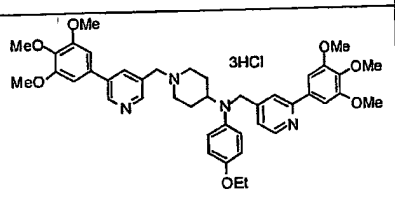
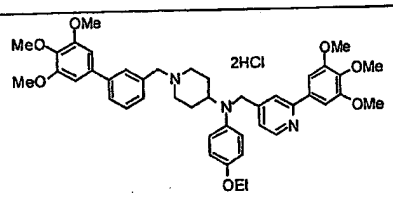


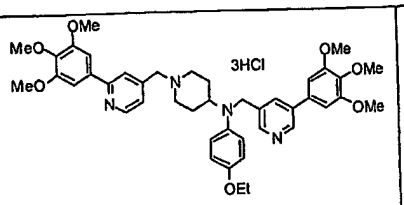
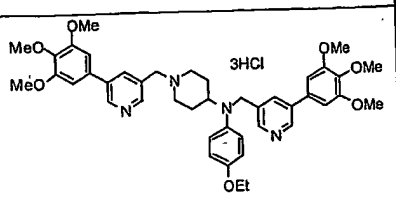
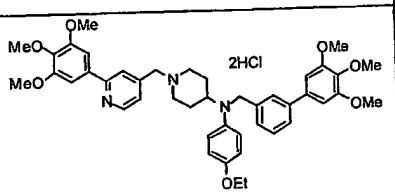
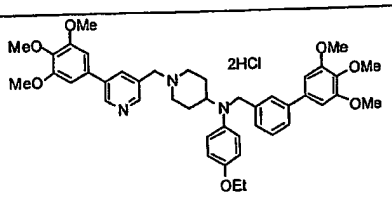
1-(tert-Butoxycarbonyl)-4-[N-(4-ethoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (1.06 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

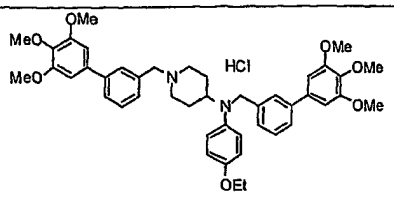
Yield: 913 mg (97%).

Examples 72 to 79

These compounds were obtained by the condensation of amines obtained in Preparation Examples 103, 105 and 107 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

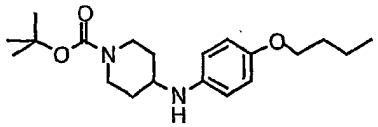
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
72		49%	1.36 (t, 3H, J=7.1Hz), 1.68-1.94 (m, 4H), 2.10-2.24 (m, 2H), 2.93-3.04 (m, 2H), 3.54-3.65 (m, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.45 (s, 2H), 6.72 (d, 2H, J=9.2 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.15 (s, 2H), 7.17 (d, 1H, J=6.1 Hz), 7.20 (dd, 1H, J=4.9 Hz, 1.0 Hz), 7.23 (s, 2H), 7.57 (s, 1H), 7.61(br, 1H), 8.54 (d, 1H, J=5.2 Hz), 8.59 (d, 1H, J=4.9 Hz).
73		63%	1.36 (t, 3H, J=7.0 Hz), 1.56-1.74 (m, 2H), 1.80-1.90 (m, 2H), 2.07-2.19 (m, 2H), 2.92-3.02 (m, 2H), 3.58 (s, 2H), 3.88-3.95 (m, 2H), 3.89 (s, 3H), 3.93 (s, 12H), 4.43 (s, 2H), 6.69-6.79 (m, 6H), 7.12-7.17 (m, 3H), 7.55 (s, 1H), 7.76 (s, 1H), 8.49 (d, 1H, J=1.8 Hz), 8.53 (d, 1H, J=5.1 Hz), 8.69 (s, 1H).
74		65%	1.36 (t, 3H, J=7.0 Hz), 1.58-1.78 (m, 2H), 1.80-1.89 (m, 2H), 2.04-2.16 (m, 2H), 2.95-3.05 (m, 2H), 3.52-3.66 (m, 1H), 3.57 (s, 1H), 3.85-3.97 (m, 2H), 3.89 (s, 6H), 3.92 (s, 6H), 3.93 (s, 6H), 4.44 (s, 2H), 6.67-6.80 (m, 6H), 7.13-7.18 (m, 3H), 7.25-7.31 (m, 1H), 7.37 (dd, 1H, J=7.6 Hz, 7.6 Hz), 7.41-7.48 (m, 2H), 7.55 (s, 1H), 8.53 (d, 1H, J=4.9 Hz).

75		42%	1.36 (t, 3H, J=7.0 Hz), 1.74-2.34 (m, 6H), 2.96-3.10 (m, 2H), 3.47-3.73 (m, 3H), 3.87-3.98 (m, 2H), 3.88 (s, 3H), 3.90 (s, 9H), 3.97 (s, 6H), 4.44 (s, 2H), 6.65 (s, 2H), 6.74-6.82 (m, 4H), 7.18-7.32 (m, 4H), 7.67 (s, 1H), 8.49 (d, 1H, J=1.6 Hz), 8.57-8.65 (m, 2H).
76		43%	1.36 (t, 3H, J=6.8 Hz), 1.63-1.96 (m, 4H), 2.00-2.26 (m, 2H), 2.92-3.03 (m, 2H), 3.44-3.66 (m, 3H), 3.86-3.96 (m, 2H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.44 (s, 2H), 6.65 (s, 2H), 6.72-6.80 (m, 6H), 7.67 (s, 1H), 7.77(br, 1H), 8.47-8.53 (m, 2H), 8.62 (d, 1H, J=1.9 Hz), 8.70 (s, 1H).
77		82%	1.35 (t, 3H, J=6.8 Hz), 1.70-1.82 (m, 2H), 1.84-1.92 (m, 2H), 2.10-2.19 (m, 2H), 2.92-3.00 (m, 2H), 3.52-3.65 (m, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (q, 2H, J=7.1 Hz), 3.96 (s, 6H), 4.47 (s, 2H), 6.70 (s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.77 (d, 2H, J=9.3 Hz), 7.18-7.28 (m, 4H), 7.33 (dd, 1H, J=7.3 Hz, 7.3 Hz), 7.37 (d, 1H, J=7.6 Hz), 7.43 (s, 1H), 7.59 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).
78		61%	1.35 (t, 3H, J=6.9 Hz), 1.58-1.80 (m, 2H), 1.82-1.91 (m, 2H), 2.09-2.18 (m, 2H), 2.93-3.20 (m, 2H), 3.56-3.65 (m, 1H), 3.58 (s, 2H), 3.87 (s, 3H), 3.89 (s, 6H), 3.89 (s, 3H), 3.91-3.94 (m, 2H), 3.93 (s, 6H), 4.45 (s, 2H), 6.69 (s, 2H), 6.71-6.78 (m, 6H), 7.23-7.28 (m, 1H), 7.32 (t, 1H, J=7.5 Hz), 7.36 (d, 1H, J=7.6 Hz), 7.42 (s, 1H), 7.77 (s, 1H), 8.49 (d, 1H, J=1.8 Hz), 8.69 (d, 1H, J=1.8 Hz).

79		73%	1.35 (t, 3H, J=6.8 Hz), 1.68-1.80 (m, 2H), 1.81-1.89 (m, 2H), 2.06-2.14 (m, 2H), 2.96-3.03 (m, 2H), 3.57 (s, 2H), 3.57-3.65 (m, 1H), 3.87 (s, 3H), 3.89 (s, 9H), 3.91-3.96 (m, 2H), 3.92 (s, 6H), 4.46 (s, 2H), 6.69-6.79 (m, 9H), 7.23-7.47 (m, 7H).

Preparation Example 108

Synthesis of 1-(tert-butoxycarbonyl)-4-(4-butoxyphenylamino)piperidine:



1-(tert-butoxycarbonyl)-4-piperidone (5.00 g) and 4-butoxyaniline (3.95 g) was treated in the same manner as described in Preparation Example 37 to give brown powder of the title compound.

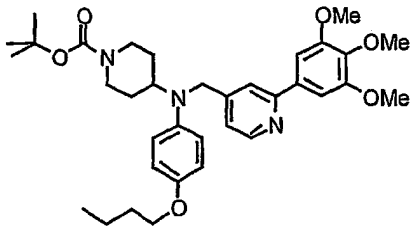
Yield: 6.91 g (83%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.96 (t, 3H, J=7.2 Hz), 1.23-1.35 (m, 2H), 1.42-1.53 (m, 2H), 1.46 (s, 9H), 1.68-1.76 (m, 2H), 1.97-2.05 (m, 2H), 2.84-2.95 (m, 2H), 3.28-3.37 (m, 1H), 3.88 (t, 2H, J=6.6 Hz), 3.96-4.12 (m, 2H), 6.57 (d, 2H, J=9.0 Hz), 6.77 (d, 2H, J=8.8 Hz).

Preparation Example 109

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-butoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-butoxyphenyl)amino]piperidine (696 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title

compound.

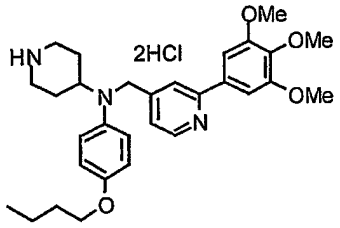
Yield: 980 mg (81%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J=7.4 Hz), 1.40-1.50 (m, 2H), 1.44 (s, 9H), 1.67-1.76 (m, 2H), 1.82-1.90 (m, 2H), 1.82-1.90 (m, 2H), 2.70-2.82 (m, 2H), 3.61-3.71 (m, 1H), 3.84-3.90 (m, 5H), 3.94 (s, 6H), 4.10-4.28 (m, 2H), 4.39 (s, 2H), 6.74 (d, 2H, J=9.4 Hz), 6.78 (d, 2H, J=9.4 Hz), 7.14-7.18 (m, 3H), 7.56 (s, 1H), 8.54 (d, 1H, J=5.1 Hz).

Preparation Example 110

Synthesis of

4-[N-(4-butoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



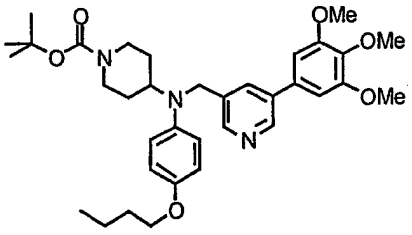
1-(tert-Butoxycarbonyl)-4-[N-(4-butoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (980 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 926 mg (99%).

Preparation Example 111

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-butoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-butoxyphenyl)amino]piperidine (697 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same

manner as described in Example 9 to give light yellow amorphous of the title compound.

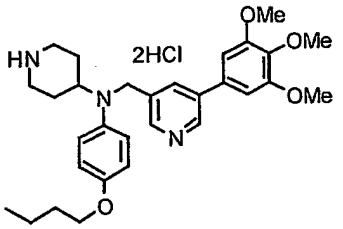
Yield: 485 mg (40%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J=7.4 Hz), 1.40-1.57 (m, 2H), 1.44 (s, 9H), 1.67-1.75 (m, 2H), 1.82-1.90 (m, 2H), 2.69-2.81 (m, 2H), 3.51-3.60 (m, 1H), 3.87 (q, 2H, J=6.6 Hz), 3.88 (s, 3H), 3.90 (s, 6H), 4.06-4.23 (m, 2H), 4.39 (s, 2H), 6.66 (s, 2H), 6.77 (d, 2H, J=9.2 Hz), 6.81 (d, 2H, J=9.2 Hz), 6.81 (d, 2H, J=9.4 Hz), 7.67 (s, 1H), 8.49 (d, 1H, J=1.8 Hz), 8.62 (d, 1H, J=2.2 Hz).

Preparation Example 112

Synthesis of

4-[N-(4-butoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



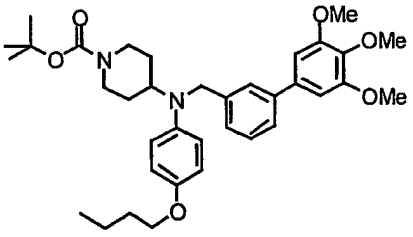
1-(tert-Butoxycarbonyl)-4-[N-(4-butoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (485 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 456 mg (98%).

Preparation Example 113

Synthesis of

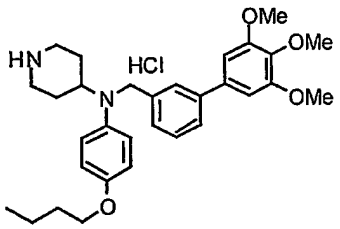
1-(tert-butoxycarbonyl)-4-[N-(4-butoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-butoxyphenyl)amino]piperidine (697 mg) and

3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 1.17 g (97%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.95 (t, 3H, J=7.3 Hz), 1.40-1.61 (m, 4H), 1.44 (s, 9H), 1.67-1.75 (m, 2H), 1.83-1.90 (m, 2H), 2.70-2.83 (m, 2H), 3.63-3.72 (m, 2H), 3.87 (q, 2H, J=6.6 Hz), 3.88 (s, 3H), 3.90 (s, 6H), 4.09-4.28 (m, 2H), 4.41 (s, 2H), 6.70 (s, 2H), 6.76 (s, 4H), 7.26 (d, 2H, J=8.0 Hz), 7.33 (t, 1H, J=7.6 Hz), 7.38 (d, 1H, J=7.3 Hz), 7.42 (s, 1H).

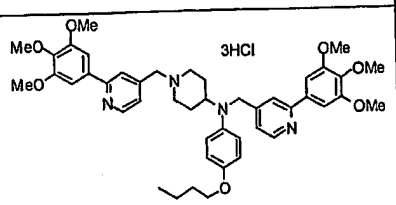
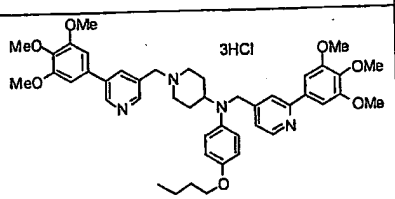
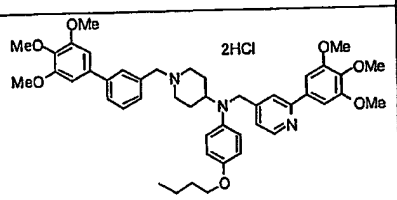
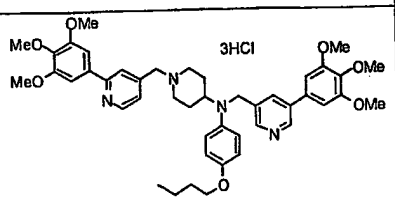
Preparation Example 114
Synthesis of
4-[N-(4-butoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

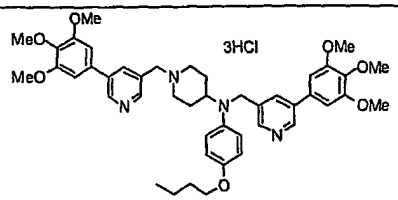
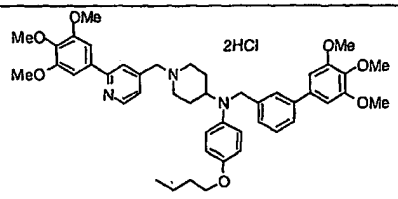
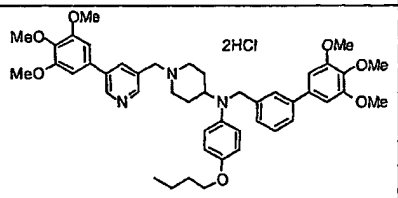
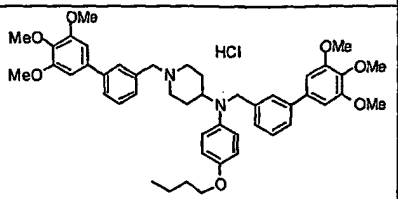


1-(tert-Butoxycarbonyl)-4-[N-(4-butoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (1.17 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 1.02 g (98%).

Example 80 to 87

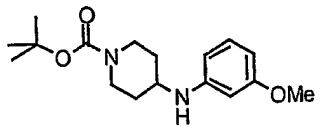
These compounds were obtained by the condensation of amines obtained in Preparation Examples 110, 112 and 114 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
80		63	0.95 (t, 3H, J=7.3 Hz), 1.40-1.51 (m, 2H), 1.66-1.79 (m, 2H), 1.83-1.92 (m, 2H), 2.10-2.21 (m, 2H), 2.92-3.02 (m, 2H), 3.53-3.63 (m, 3H), 3.84-3.90 (m, 2H), 3.89 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 6.72 (d, 2H, J=9.3 Hz), 6.77 (d, 2H, J=9.3 Hz), 7.15 (s, 2H), 7.17 (d, 1H, J=5.1 Hz), 7.20 (d, 1H, J=6.1 Hz), 7.22 (s, 2H), 7.57 (s, 1H), 7.59 (s, 1H), 8.54 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=5.1 Hz).
81		44%	0.95 (t, 3H, J=7.4 Hz), 1.42-1.51 (m, 2H), 1.67-1.76 (m, 4H), 1.80-1.91 (m, 2H), 2.08-2.20 (m, 2H), 2.92-3.03 (m, 2H), 3.84-3.96 (m, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 12H), 4.43 (s, 2H), 6.69-6.79 (m, 6H), 7.14 (s, 2H), 7.16 (d, 1H, J=5.2 Hz), 7.55 (s, 1H), 7.76 (s, 1H), 8.49 (d, 1H, J=1.8 Hz), 8.53 (d, 1H, J=5.0 Hz), 8.69 (s, 1H).
82		53%	0.95 (t, 3H, J=7.2 Hz), 1.40-1.51 (m, 2H), 1.65-1.78 (m, 4H), 1.81-1.89 (m, 2H), 2.05-2.18 (m, 2H), 3.05-3.06 (m, 2H), 3.54-3.65 (m, 3H), 3.84-3.96 (m, 20H), 4.44 (s, 2H), 6.70 (d, 2H, J=9.2 Hz), 6.74-6.80 (m, 4H), 7.11-7.19 (m, 3H), 7.22-7.32 (m, 1H), 7.34-7.50 (m, 3H), 7.55 (s, 1H), 8.53 (d, 1H, J=5.1 Hz).
83		42%	0.95 (t, 3H, 7.4Hz), 1.40-1.51 (m, 2H), 1.67-1.86 (m, 6H), 2.03-2.30 (m, 2H), 2.92-3.06 (m, 2H), 3.46-3.56 (m, 1H), 3.60 (s, 2H), 3.84-3.91 (m, 2H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.44 (s, 2H), 6.65 (s, 2H), 6.74-6.81 (m, 4H), 7.20 (d, 1H, J=4.9 Hz), 7.25 (s, 2H), 7.67(br, 2H), 8.50 (d, 1H, J=1.6 Hz), 8.60 (d, 1H, J=5.6 Hz).

84		36%	0.95 (t, 3H, J=7.4 Hz), 1.40-1.51 (m, 2H), 1.66-1.79 (m, 4H), 1.82-1.92 (m, 2H), 2.00-2.22 (m, 2H), 2.83-3.06 (m, 2H), 3.44-3.67 (m, 3H), 3.82-3.97 (m, 2H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.44 (s, 2H), 6.65 (s, 2H), 6.72-6.80 (m, 6H), 7.67 (s, 1H), 7.76(br, 1H), 8.47-8.53 (m, 2H), 8.62 (d, 1H, J=2.2 Hz), 8.70 (s, 1H).
85		72%	0.95 (t, 3H, J=7.3 Hz), 1.40-1.51 (m, 2H), 1.66-1.82 (m, 4H), 1.84-1.92 (m, 2H), 2.10-2.20 (m, 2H), 2.92-3.00 (m, 2H), 3.53-3.66 (m, 3H), 3.83-3.92 (m, 2H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.47 (s, 2H), 6.67 (s, 2H), 6.73 (d, 2H, J=9.2 Hz), 6.77 (d, 2H, J=9.5 Hz), 7.18-7.29 (m, 4H), 7.33 (dd, 1H, J=7.3 Hz, 7.3 Hz), 7.37 (d, 1H, J=7.6 Hz), 7.43 (s, 1H), 7.60 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).
86		24%	0.94 (t, 3H, J=7.4 Hz), 1.41-1.51 (m, 2H), 1.61-1.80 (m, 4H), 1.82-1.92 (m, 2H), 2.08-2.19 (m, 2H), 2.92-3.02 (m, 2H), 3.55-3.65 (m, 1H), 3.57 (s, 2H), 3.84-3.91 (m, 2H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.93 (s, 6H), 4.45 (s, 2H), 6.69 (s, 2H), 6.71-6.78 (m, 4H), 6.75 (s, 2H), 7.23-7.28 (m, 1H), 7.32 (t, 1H, J=7.4 Hz), 7.36 (d, 1H, J=7.6 Hz), 7.42 (s, 1H), 7.77 (s, 1H), 8.49 (d, 1H, J=1.6 Hz), 8.69 (s, 1H).
87		78%	0.94 (t, 3H, J=7.3 Hz), 1.40-1.50 (m, 2H), 1.66-1.88 (m, 4H), 1.82-1.89 (m, 2H), 2.04-2.16 (m, 2H), 2.96-3.03 (m, 2H), 3.55-3.65 (m, 3H), 3.83-3.90 (m, 2H), 3.87 (s, 3H), 3.89 (s, 9H), 3.92 (s, 6H), 4.46 (s, 2H), 6.69-6.79 (m, 9H), 7.23-7.48 (m, 7H).

Preparation Example 115

Synthesis of 4-(*m*-anisidino)-1-(tert-butoxycarbonyl)piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (4.78 g) and *m*-anisidine (2.96 g) were condensed in the same manner as described in Preparation Example 37 to give the title compound.

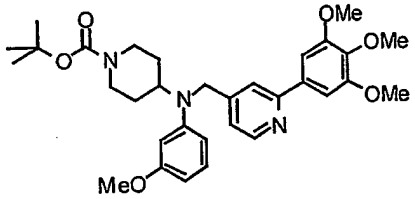
Yield: 4.83 g (66%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.20-1.39 (m, 2H), 1.44 (s, 9H), 1.99-2.05 (m, 2H), 2.89 (dt, 2H, J=13.5 Hz, 2.2 Hz), 3.33-3.44 (m, 1H), 3.75 (s, 3H), 3.96-4.07 (m, 2H), 6.14 (t, 1H, J=2.2 Hz), 6.18-6.29 (m, 2H), 7.05 (t, 1H, J=8.1 Hz).

Preparation Example 116

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(3-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



4-(*m*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

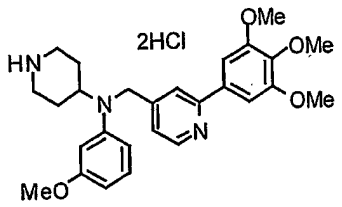
Yield: 789 mg (70%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.50-1.67 (m, 2H), 1.82-1.91 (m, 2H), 2.74-2.87 (m, 2H), 3.74 (s, 3H), 3.88-3.98 (m, 1H), 3.89 (s, 3H), 3.94 (s, 6H), 4.14-4.32 (m, 2H), 4.48 (s, 2H), 6.28 (dd, 1H, J=2.2 Hz, 2.2 Hz), 6.31-6.37 (m, 2H), 7.10-7.15 (m, 2H), 7.16 (s, 2H), 7.55 (s, 1H), 8.56 (d, 1H, J=5.1 Hz).

Preparation Example 117

Synthesis of

4-[N-(3-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]pip eridine dihydrochloride:

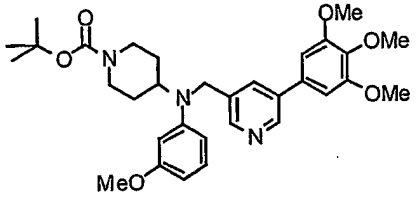


1-(tert-Butoxycarbonyl)-4-[N-(3-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphe nyl)pyridin-4-yl]methyl]amino]piperidine (789 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 710 mg (95%).

Preparation Example 118

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(3-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridi n-5-yl]methyl]amino]piperidine:

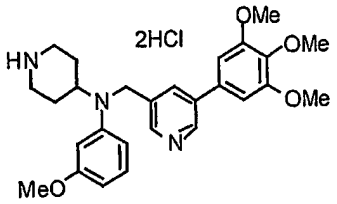


4-(*m*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 396 mg (35%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.54-1.66 (m, 2H), 1.81-1.91 (m, 2H), 2.73-2.87 (m, 2H), 3.74 (s, 3H), 3.87-3.93 (m, 1H), 3.88 (s, 3H), 3.90 (s, 6H), 4.14-4.29 (m, 2H), 4.51 (s, 2H), 6.30-6.35 (m, 2H), 6.38 (d, 1H, J=7.2 Hz), 6.68 (s, 2H), 7.12 (dd, 1H, J=8.8 Hz, 8.8 Hz), 7.66 (s, 1H), 8.49 (d, 1H, J=2.0 Hz), 8.66 (d, 1H, J=2.2 Hz).

Preparation Example 119

Synthesis of

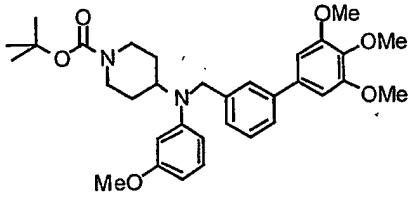
4-[N-(3-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]pip eridine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(3-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (396 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 348 mg (92%).

Preparation Example 120

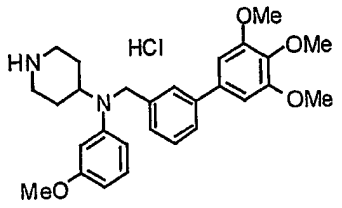
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(3-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



4-(*m*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Preparation Example 9 to give light yellow amorphous of the title compound.
Yield: 1.01 g (90%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.56-1.67 (m, 2H), 1.83-1.91 (m, 2H), 2.72-2.86 (m, 2H), 3.73 (s, 3H), 3.85-3.98 (m, 1H), 3.88 (s, 3H), 3.90 (s, 6H), 4.12-4.30 (m, 2H), 4.50 (s, 2H), 6.27-6.34 (m, 2H), 6.38 (dd, 1H, J=8.2 Hz, 2.4 Hz), 6.72 (s, 2H), 7.10 (dd, 1H, J=8.2 Hz, 8.2 Hz), 7.21-7.27 (m, 1H), 7.32-7.43 (m, 3H).

Preparation Example 121

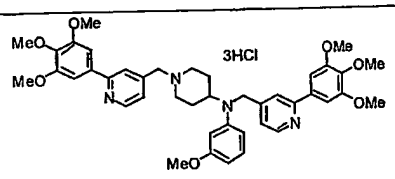
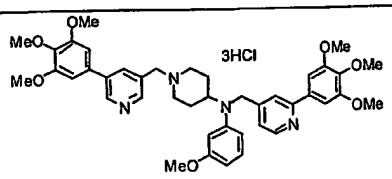
Synthesis of
4-[N-(3-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

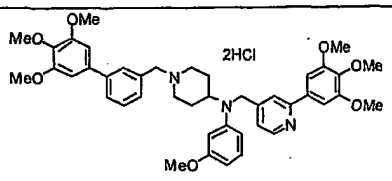
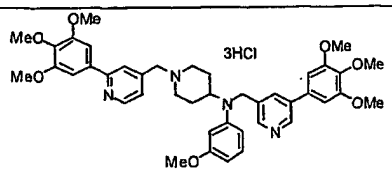
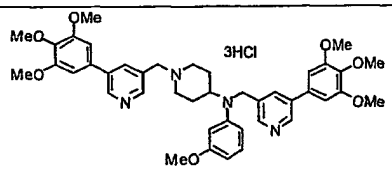
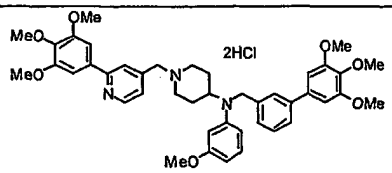


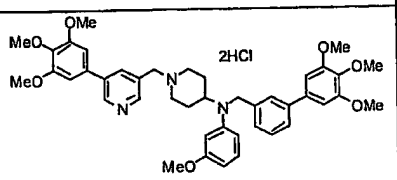
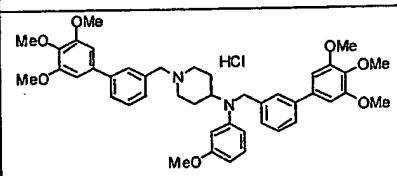
1-(tert-Butoxycarbonyl)-4-[N-(3-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (1.01 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 820 mg (92%).

Examples 88 to 95

These compounds were obtained by the condensation of amines obtained in Preparation Examples 117, 119 and 121 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

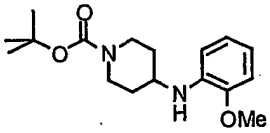
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
88		63%	1.70-1.82 (m, 2H), 1.83-1.90 (m, 2H), 2.14-2.23 (m, 2H), 2.94-3.01 (m, 2H), 3.57 (s, 2H), 3.73 (s, 3H), 3.76-3.88 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.53 (s, 2H), 6.26-6.35 (m, 3H), 7.11 (dd, 1H, J=8.3 Hz, 8.3 Hz), 7.12-7.14 (m, 1H), 7.15 (s, 2H), 7.20 (d, 1H, J=5.1 Hz), 7.22 (s, 2H), 7.55 (s, 1H), 7.58 (s, 1H), 8.55 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=4.9 Hz).
89		72%	1.67-1.90 (m, 4H), 2.13-2.22 (m, 2H), 2.94-3.04 (m, 2H), 3.59 (s, 2H), 3.74 (s, 3H), 3.77-3.87 (m, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.52 (s, 2H), 6.27 (dd, 1H, J=2.4 Hz, 2.4 Hz), 6.29-6.34 (m, 2H), 6.75 (s, 2H), 7.08-7.17 (m, 4H), 7.54 (s, 1H), 7.75 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.54 (d, 1H, J=5.1 Hz),

			8.69 (d, 1H, J=2.0 Hz).
90		60%	1.68-1.90 (m, 4H), 2.09-2.19 (m, 2H), 2.97-3.06 (m, 2H), 3.58 (s, 2H), 3.73 (s, 3H), 3.76-3.87 (m, 1H), 3.89 (s, 6H), 3.92 (s, 6H), 3.92 (s, 6H), 4.52 (s, 2H), 6.25-6.35 (m, 3H), 6.76 (s, 2H), 6.78-7.17 (m, 4H), 7.25-7.32 (m, 1H), 7.37 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.41-7.47 (m, 2H), 7.54 (s, 1H), 8.54 (d, 1H, J=5.1 Hz).
91		50%	1.80-1.93 (m, 4H), 2.13-2.32 (m, 2H), 2.87-3.10 (m, 2H), 3.60 (s, 1H), 3.69-3.85 (m, 1H), 3.73 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.57 (s, 2H), 6.29-6.34 (m, 2H), 6.37 (dd, 1H, J=8.2 Hz, 8.1 Hz), 6.67 (s, 2H), 7.11 (dd, 1H, J=8.6 Hz, 8.6 Hz), 7.20-7.28 (m, 3H), 7.58-7.72 (m, 1H), 7.68 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.60 (d, 1H, J=4.7 Hz), 8.65 (d, 1H, J=2.0 Hz).
92		35%	1.70-1.90 (m, 4H), 2.12-2.25 (m, 2H), 2.95-3.03 (m, 2H), 3.59 (s, 2H), 3.72-3.97 (m, 1H), 3.73 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.54 (s, 2H), 6.25-6.38 (m, 2H), 6.36 (d, 1H, J=8.4 Hz, 8.4 Hz), 6.67 (s, 2H), 6.75 (s, 2H), 7.11 (dd, 1H, J=8.4 Hz), 7.66 (s, 1H), 8.49 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.64 (d, 1H, J=2.0 Hz), 8.70 (d, 1H, J=1.9 Hz).
93		86%	1.73-1.93 (m, 4H), 2.13-2.23 (m, 2H), 2.94-3.02 (m, 2H), 3.57 (s, 2H), 3.73 (s, 3H), 3.77-3.87 (m, 1H), 3.88 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.56 (s,2H), 6.27 (dd, 1H, J=8.0 Hz, 2.2 Hz), 6.31 (dd, 1H, J=2.2 Hz, 2.2 Hz), 6.36 (dd, 1H, J=8.2 Hz, 2.2 Hz), 6.71 (s, 2H), 7.09 (dd, 1H, J=8.1 Hz, 8.1 Hz), 7.18-7.28 (m, 4H), 7.34 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.38 (d, 1H, J=7.6 Hz), 7.42

			(s, 1H), 7.59 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).
94		56%	1.72-1.92 (m, 4H), 2.10-2.23 (m, 2H), 2.92-3.60 (m, 2H), 3.59 (s, 2H), 3.72 (s, 3H), 3.77-3.89 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.93 (s, 6H), 4.55 (s, 2H), 6.27 (dd, 1H, J=8.0 Hz, 2.2 Hz), 6.31 (dd, 1H, J=2.1 Hz, 2.1 Hz), 6.36 (dd, 1H, J=8.4 Hz, 2.4 Hz), 6.70 (s, 2H), 6.75 (s, 2H), 7.09 (dd, 1H, J=8.2 Hz, 8.2 Hz), 7.22 (d, 1H, J=7.4 Hz), 7.33 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.38 (d, 1H, J=7.8 Hz), 7.40 (s, 1H), 7.77 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.69 (d, 1H, J=1.8 Hz).
95		77%	1.66-1.89 (m, 4H), 2.08-2.18 (m, 2H), 2.95-3.05 (m, 2H), 3.58 (s, 2H), 3.72 (s, 3H), 3.75-3.84 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 6H), 4.55 (s, 2H), 6.26 (dd, 1H, J=8.0 Hz, 2.2 Hz), 6.30 (dd, 1H, J=2.2 Hz, 2.2 Hz), 6.36 (dd, 1H, J=8.3 Hz, 2.2 Hz), 6.70 (s, 2H), 6.76 (s, 2H), 7.08 (dd, 1H, J=8.3 Hz, 8.3 Hz), 7.22 (d, 1H, J=7.3 Hz), 7.27-7.47 (m, 7H).

Preparation Example 122

Synthesis of 4-(*o*-anisidino)-1-(tert-butoxycarbonyl)piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (4.78 g) and *o*-anisidine (2.96 g) were condensed in the same manner as described in Preparation Example 37 to give the title compound.

Yield: 2.61 g (36%).

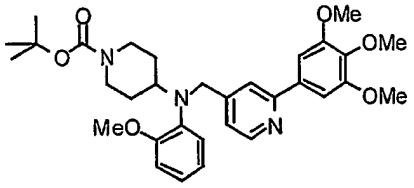
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31-1.41 (m, 2H), 1.47 (s, 9H), 2.00-2.08 (m, 2H), 2.90-3.01 (m, 2H), 3.38-3.47 (m, 1H), 3.83 (s, 3H), 4.00-4.21 (m, 2H), 6.60-6.69 (m,

2H), 6.76-6.89 (m, 2H).

Preparation Example 123

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(2-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



4-(*o*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

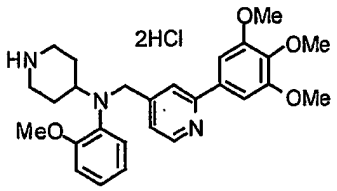
Yield: 763 mg (68%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41-1.58 (m, 2H), 1.44 (s, 9H), 1.81-1.91 (m, 2H), 2.62-2.78 (m, 2H), 3.29 (tt, 1H, J=7.6 Hz, 3.7 Hz), 3.86 (s, 3H), 3.89 (s, 3H), 3.95 (s, 6H), 4.06-4.16 (m, 2H), 4.37 (s, 2H), 6.80 (ddd, 1H, J=7.6 Hz, 7.6 Hz, 1.2 Hz), 6.87 (dd, 1H, J=8.5 Hz, 1.0 Hz), 7.00-7.06 (m, 2H), 7.14 (s, 2H), 7.20 (dd, 1H, J=4.9 Hz, 1.0 Hz), 7.61 (s, 1H), 8.49 (d, 1H, J=4.9 Hz).

Preparation Example 124

Synthesis of

4-[N-(2-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



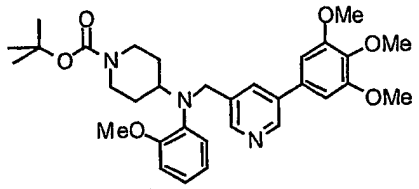
1-(tert-Butoxycarbonyl)-4-[N-(2-methoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (763 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 701 mg (97%).

Preparation Example 125

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(2-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



4-(*o*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

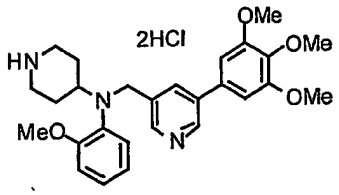
Yield: 353 mg (31%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.46-1.53 (m, 2H), 1.82-1.91 (m, 2H), 2.62-2.78 (m, 2H), 3.24-3.33 (m, 1H), 3.83 (s, 3H), 3.89 (s, 3H), 3.91 (s, 6H), 4.03-4.16 (m, 2H), 4.37 (s, 2H), 6.64 (s, 2H), 6.79 (ddd, 1H, J=7.6 Hz, 7.6 Hz, 1.2 Hz), 6.84 (dd, 1H, J=7.0 Hz, 1.2 Hz), 6.97-7.06 (m, 2H), 7.68 (dd, 1H, J=1.3 Hz, 1.3 Hz), 8.49 (d, 1H, J=2.0 Hz), 8.56 (d, 1H, J=2.2 Hz).

Preparation Example 126

Synthesis of

4-[N-(2-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



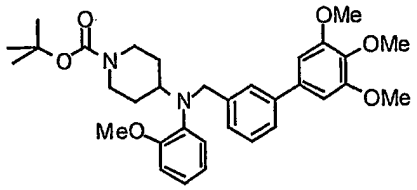
1-(tert-Butoxycarbonyl)-4-[N-(2-methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (353 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 312 mg (93%).

Preparation Example 127

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(2-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl] amino]piperidine:



4-(*o*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (613 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

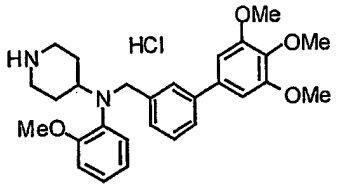
Yield: 1.12 g (100%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 9H), 1.46-1.57 (m, 2H), 1.81-1.90 (m, 2H), 2.62-2.76 (m, 2H), 3.31 (tt, 1H, J=11.1 Hz, 3.3 Hz), 3.84 (s, 3H), 3.88 (s, 3H), 3.91 (s, 6H), 4.00-4.16 (m, 2H), 4.36 (s, 2H), 6.67 (s, 2H), 6.78 (t, 1H, J=7.3 Hz), 6.85 (d, 1H, J=7.9 Hz), 6.96-7.03 (m, 2H), 7.24-7.34 (m, 3H), 7.43 (s, 1H).

Preparation Example 128

Synthesis of

4-[N-(2-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:



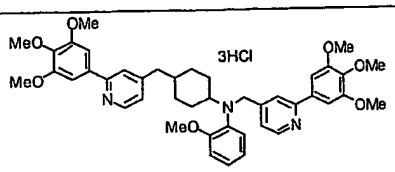
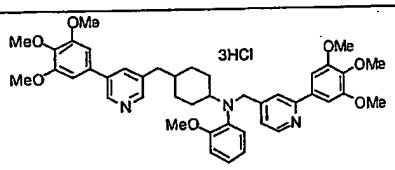
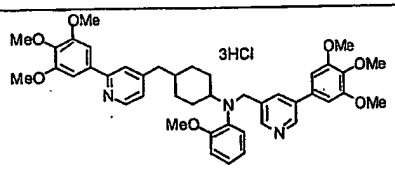
1-(tert-Butoxycarbonyl)-4-[N-(2-methoxyphenyl)-N-[3-(3,4,5-trimethoxyphen yl)benzyl]amino]piperidine (1.12 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

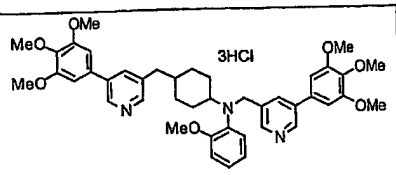
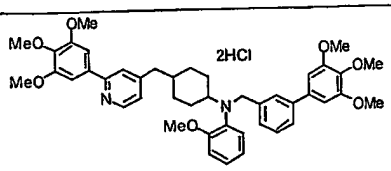
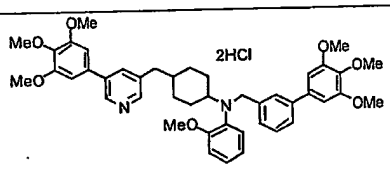
Yield: 987 mg (99%).

Example 96 to 101

These compounds were obtained by the condensation of amines obtained in Preparation Examples 124, 126 and 128 with chloride derivatives obtained in

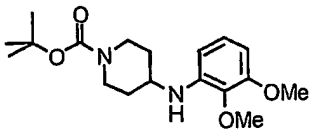
Preparation Examples 3 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
96		73%	1.62-1.74 (m, 2H), 1.82-1.90 (m, 2H), 1.98-2.08 (m, 2H), 2.86-2.94 (m, 2H), 3.13-3.22 (m, 1H), 3.52 (s, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.94 (s, 6H), 3.96 (s, 6H), 4.40 (s, 2H), 6.80 (ddd, 1H, J=7.6 Hz, 7.6 Hz, 1.2 Hz), 6.86 (dd, 1H, J=8.1 Hz,1.2 Hz), 6.98-7.05 (m, 1H), 7.14 (s, 2H), 7.18 (dd, 1H, J=4.9 Hz, 1.2 Hz), 7.20-7.24 (m, 1H), 7.22 (s, 2H), 7.58 (s, 1H), 7.62 (s, 1H), 8.49 (d, 1H, J=4.9 Hz), 8.57 (d, 1H, J=5.2 Hz).
97		55%	1.60-1.73 (m, 4H), 1.82-1.93 (m, 2H), 1.98-2.07 (m, 2H), 2.87-2.97 (m, 2H), 3.12-3.22 (m, 1H), 3.54 (s, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.94 (s, 6H), 4.39 (s, 2H), 6.75 (s, 2H), 6.79 (dd, 1H, J=7.4 Hz, 7.4 Hz), 6.86 (d, 1H, J=7.8 Hz), 6.97-7.05 (m, 2H), 7.13 (s, 2H), 7.20 (d, 1H, J=4.7 Hz), 7.61 (s, 1H), 7.75 (s, 1H), 8.46-8.50 (m, 2H), 8.68 (d, 1H, J=2.0 Hz).
98		29%	1.64-1.82 (m, 2H), 1.84-1.97 (m, 2H), 2.00-2.15 (m, 2H), 2.84-3.01 (m, 2H), 3.13-3.27 (m, 1H), 3.56 (s, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.96 (s, 6H), 4.40 (s, 2H), 6.63 (s, 2H), 6.75-6.88 (m, 2H), 6.97-7.04 (m, 2H), 7.19 (d, 1H, J=4.3 Hz), 7.25 (s, 2H), 7.58-7.73 (m, 2H), 8.50 (d, 1H, J=1.6 Hz), 8.56 (d, 1H, J=2.2 Hz), 8.58 (d, 1H, J=4.9 Hz).

99		30%	1.62-1.75 (m, 2H), 1.83-1.94 (m, 2H), 1.95-2.11 (m, 2H), 2.84-3.01 (m, 2H), 3.12-3.23 (m, 1H), 3.55 (s, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.90 (s, 6H), 3.93 (s, 6H), 4.39 (s, 2H), 6.63 (s, 2H), 6.70-6.86 (m, 4H), 6.94-7.06 (m, 2H), 7.68 (s, 1H), 7.76 (s, 1H), 8.47 (d, 1H, J=1.7 Hz), 8.49 (d, 1H, J=1.7 Hz), 8.55 (d, 1H, J=2.2 Hz), 8.69 (s, 1H).
100		67%	1.64-1.79 (m, 2H), 1.85-1.93 (m, 2H), 1.99-2.09 (m, 2H), 2.86-2.95 (m, 2H), 3.16-3.26 (m, 1H), 3.52 (s, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 3.90 (s, 6H), 3.96 (s, 6H), 4.40 (s, 2H), 6.67 (s, 2H), 6.78 (dd, 1H, J=7.4 Hz, 7.4 Hz), 6.85 (d, 1H, J=8.2 Hz), 6.97 (dd, 1H, J=7.8 Hz, 7.8 Hz), 7.02 (dd, 1H, J=7.8, 1.6 Hz), 7.17-7.33 (m, 6H), 7.44 (s, 1H), 7.59 (s, 1H), 8.57 (d, 1H, J=5.1 Hz).
101		55%	1.62-1.77 (m, 2H), 1.82-1.94 (m, 2H), 1.98-2.08 (m, 2H), 2.86-2.96 (m, 2H), 3.16-3.26 (m, 1H), 3.54 (s, 2H), 3.83 (s, 3H), 3.87 (s, 3H), 3.90 (s, 9H), 3.93 (s, 6H), 4.39 (s, 2H), 6.66 (s, 2H), 6.73-6.80 (m, 3H), 6.84 (d, 1H, J=7.8 Hz), 6.97 (dd, 1H, J=7.8 Hz, 7.8 Hz), 7.01 (d, 1H, J=7.8 Hz), 7.23-7.32 (m, 3H), 7.43 (s, 1H), 7.77 (s, 1H), 8.47 (d, 1H, J=1.4 Hz), 8.68 (d, 1H, J=1.8 Hz).

Preparation Example 129

Synthesis of 1-(tert-butoxycarbonyl)-4-(2,3-dimethoxyphenylamino)piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (4.78 g) and 2,3-dimethoxyaniline (3.68 g) were condensed in the same manner as described in Preparation Example 37 to give

the title compound.

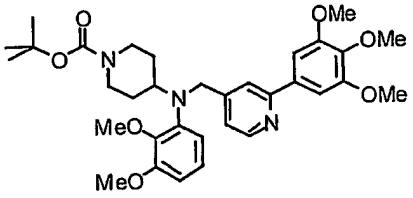
Yield: 3.18 g (39%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.29-1.42 (m, 2H), 1.45 (s, 9H), 1.97-2.03 (m, 2H), 2.92 (dt, 2H, J=13.5 Hz, 2.2 Hz), 3.38 (dt, 1H, J=13.8 Hz, 4.1 Hz), 3.77 (s, 3H), 3.82 (s, 3H), 3.99-4.03 (m, 2H), 4.17 (m, 1H), 6.27-6.32 (m, 2H), 6.88 (t, 1H, J=8.4 Hz).

Preparation Example 130

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(2,3-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-(2,3-dimethoxyphenylamino)piperidine (673 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

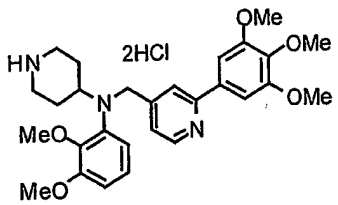
Yield: 613 mg (52%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.56-1.70 (m, 2H), 1.84-1.91 (m, 2H), 2.62-2.76 (m, 2H), 3.58 (tt, 1H, J=11.8 Hz, 3.6 Hz), 3.83 (s, 3H), 3.89 (s, 6H), 3.93 (s, 6H), 4.08-4.25 (m, 2H), 4.35 (s, 2H), 6.56-6.63 (m, 2H), 6.86 (t, 1H, J=8.3 Hz), 7.14 (s, 2H), 7.17 (dd, 1H, J=5.1 Hz, 1.2 Hz), 7.62 (s, 1H), 8.50 (d, 1H, J=5.1 Hz).

Preparation Example 131

Synthesis of

4-[N-(2,3-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(2,3-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxy

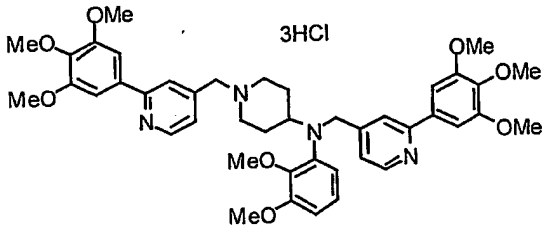
phenyl)pyridin-4-yl]methyl]amino]piperidine (613 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 512 mg (88%).

Example 102

Synthesis of

4-[N-(2,3-dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



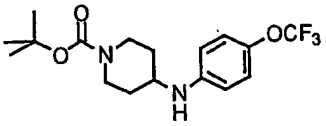
4-[N-(2,3-Dimethoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride (113 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (59 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as light yellow powder after converting a free base to a trihydrochloride.

Yield: 21 mg (12%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ: 1.76-1.96 (m, 4H), 2.00-2.13 (m, 2H), 2.86-3.00 (m, 2H), 3.42-3.60 (m, 1H), 3.54 (s, 2H), 3.82 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.97 (s, 6H), 4.41 (s, 2H), 6.57 (d, 1H, J=8.0 Hz), 6.62 (d, 1H, J=8.2 Hz), 6.85 (dd, 1H, J=8.4 Hz, 8.4 Hz), 7.11-7.29 (m, 6H), 7.59 (s, 1H), 7.63 (s, 1H), 8.50 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 132

Synthesis of 1-(tert-butoxycarbonyl)-4-[[4-(trifluoromethoxy)phenyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 4-(trifluoromethoxy)aniline

(4.23 g) was treated in the same manner as described in Preparation Example 37 to give white powder of the title compound.

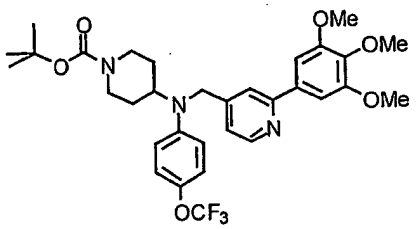
Yield: 5.22 g (60%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25-1.40 (m, 2H), 1.47 (s, 9H), 1.98-2.08 (m, 2H), 2.83-2.98 (m, 2H), 3.34-3.43 (m, 1H), 3.97-4.12 (m, 2H), 6.58 (d, 2H, J=8.8 Hz), 7.03 (d, 2H, J=8.8 Hz).

Preparation Example 133

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(trifluoromethoxy)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(trifluoromethoxy)phenyl]amino]piperidine (721 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

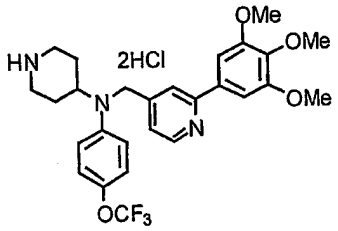
Yield: 543 mg (44%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.52-1.66 (m, 2H), 1.81-1.91 (m, 2H), 2.73-2.88 (m, 2H), 3.88-3.99 (m, 1H), 3.89 (s, 3H), 3.93 (s, 6H), 4.15-4.34 (m, 2H), 4.48 (s, 2H), 6.68 (d, 2H, J=9.2 Hz), 7.07 (d, 2H, J=8.6 Hz), 7.12 (dd, 1H, J=5.2 Hz, 1.3 Hz), 7.15 (s, 2H), 7.52 (s, 1H), 8.58 (d, 1H, J=5.2 Hz).

Preparation Example 134

Synthesis of

4-[N-[4-(trifluoromethoxy)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



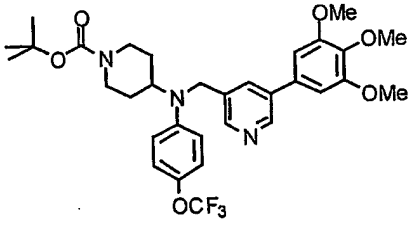
1-(tert-Butoxycarbonyl)-4-[N-[4-(trifluoromethoxy)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (543 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 481 mg (93%).

Preparation Example 135

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(trifluoromethoxy)phenyl]-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(trifluoromethoxy)phenyl]amino]piperidine (721 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

Yield: 201 mg (16%).

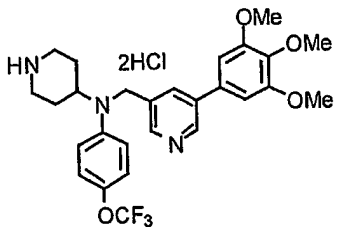
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.54-1.67 (m, 2H), 1.82-1.90 (m, 2H), 2.74-2.86 (m, 2H), 3.84-3.91 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.16-4.30 (m, 2H), 4.52 (s, 2H), 6.67 (s, 2H), 6.72 (d, 2H, J=9.4 Hz), 7.06 (d, 2H, J=8.4 Hz), 7.64 (t, 1H, J=2.1 Hz), 8.49 (d, 1H, J=2.2 Hz), 8.68 (d, 1H, J=2.1 Hz).

Preparation Example 136

Synthesis of

4-[N-[4-(trifluoromethoxy)phenyl]-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]

amino]piperidine dihydrochloride:



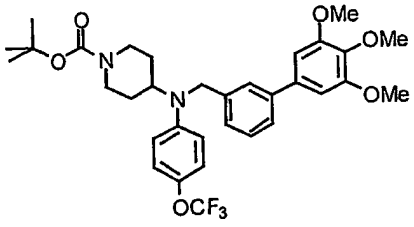
1-(tert-Butoxycarbonyl)-4-[N-[4-(trifluoromethoxy)phenyl]-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (201 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 185 mg (96%).

Preparation Example 137

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(trifluoromethoxy)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino)piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(trifluoromethoxy)phenyl]amino]piperidine (721 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

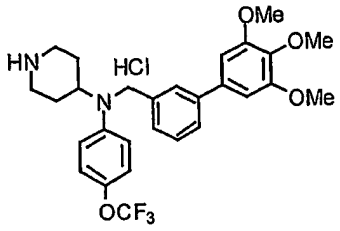
Yield: 1.06 mg (86%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.56-1.68 (m, 2H), 1.83-1.90 (m, 2H), 2.71-2.86 (m, 2H), 3.87-3.90 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.16-4.29 (m, 2H), 4.51 (s, 2H), 6.70 (d, 2H, J=9.3 Hz), 6.70 (s, 2H), 7.04 (d, 2H, J=8.5 Hz), 7.22 (d, 1H, J=7.8 Hz), 7.34-7.44 (m, 3H).

Preparation Example 138

Synthesis of

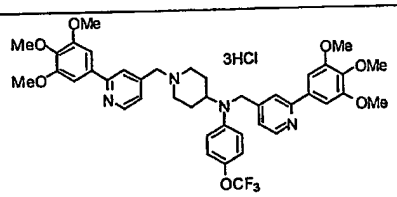
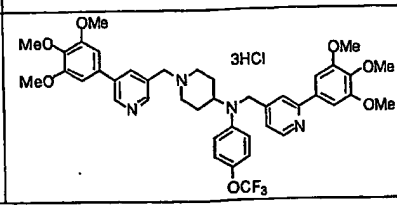
4-[N-[4-(trifluoromethoxy)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperid ine hydrochloride:

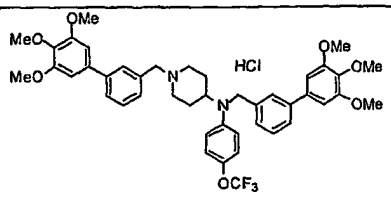
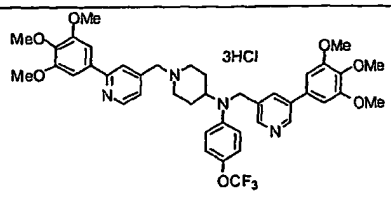
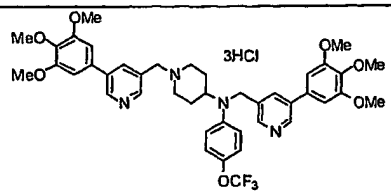
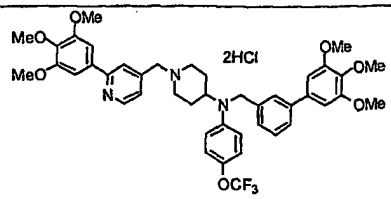


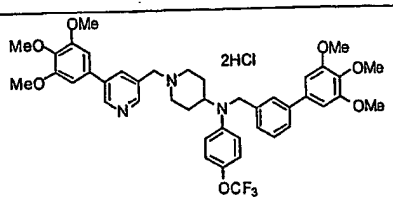
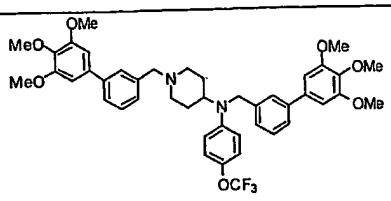
1-(tert-Butoxycarbonyl)-4-[N-[4-(trifluoromethoxy)phenyl]-N-[3-(3,4,5-trimet hoxyphenyl)benzyl]amino]piperidine (1.06 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound. Yield: 795 mg (84%).

Example 103 to 110

These compounds were obtained by the condensation of amines obtained in Preparation Examples 134, 136 and 138 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

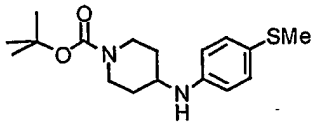
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
103		70%	1.71-1.90 (m, 4H), 2.15-2.23 (m, 2H), 2.95-3.02 (m, 2H), 3.58 (s, 2H), 3.76-3.85 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.96 (s, 6H), 4.54 (s, 2H), 6.66 (d, 2H, J=9.3 Hz), 7.05 (d, 2H, J=8.5 Hz), 7.13 (dd, 1H, J=5.1 Hz, 1.2 Hz), 7.14 (s, 2H), 7.20 (dd, 1H, J=4.9 Hz, 1.2 Hz), 7.22 (s, 2H), 7.53 (s, 1H), 7.59 (s, 1H), 8.57 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=5.2 Hz).
104		48%	1.68-1.92 (m, 4H), 2.13-2.25 (m, 2H), 2.95-3.06 (m, 2H), 3.60 (s, 2H), 3.75-3.87 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.93 (s, 6H), 4.52 (s, 2H), 6.65 (d,

			2H, J=9.4 Hz), 6.75 (s, 2H), 7.05 (d, 2H, J=9.2 Hz), 7.12 (d, 1H, J=5.1 Hz), 7.14 (s, 2H), 7.52 (s, 1H), 7.76 (s, 1H), 8.51 (d, 1H, J=1.8 Hz), 8.57 (d, 1H, J=5.1 Hz), 8.70 (d, 1H, J=2.1 Hz).
105		69%	1.70-1.89 (m, 4H), 2.10-2.19 (m, 2H), 2.98-3.08 (m, 2H), 3.59 (s, 2H), 3.72-3.84 (m, 1H), 3.89 (s, 6H), 3.92 (s, 6H), 3.92 (s, 6H), 4.52 (s, 2H), 6.65 (d, 2H, J=9.4 Hz), 6.76 (s, 2H), 7.04 (d, 2H, J=8.6 Hz), 7.11 (d, 1H, J=5.1 Hz), 7.14 (s, 2H), 7.25-7.33 (m, 1H), 7.37 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.41-7.48 (m, 2H), 7.51 (s, 1H), 8.56 (d, 1H, J=5.1 Hz).
106		41%	1.73-1.93 (m, 4H), 2.12-2.26 (m, 2H), 2.93-3.07 (m, 2H), 3.53-3.65 (m, 2H), 3.74-3.84 (m, 1H), 3.88 (s, 9H), 3.90 (s, 3H), 3.96 (s, 6H), 4.58 (s, 2H), 6.66 (s, 2H), 6.69 (d, 2H, J=9.2 Hz), 7.05 (d, 2H, J=8.8 Hz), 7.18-7.29 (m, 3H), 7.59(br, 1H), 7.64 (s, 1H), 8.49 (s, 1H), 8.60 (d, 1H, J=5.3 Hz), 8.67 (d, 1H, J=2.0 Hz).
107		28%	1.72-1.91 (m, 4H), 2.12-2.28 (m, 2H), 2.94-3.06 (m, 2H), 3.60 (s, 2H), 3.76-3.82 (m, 1H), 3.88 (s, 9H), 3.90 (s, 3H), 3.93 (s, 6H), 4.56 (s, 2H), 6.65 (s, 2H), 6.69 (d, 2H, J=9.2 Hz), 6.75 (s, 2H), 7.05 (d, 2H, J=8.8 Hz), 7.63 (s, 1H), 7.76 (s, 1H), 8.48 (d, 1H, J=1.8 Hz), 8.51 (d, 1H, J=1.8 Hz), 8.66 (d, 1H, J=2.2 Hz), 8.70 (d, 1H, J=2.2 Hz).
108		78%	1.76-1.91 (m, 4H), 2.14-2.23 (m, 2H), 2.94-3.03 (m, 2H), 3.57 (s, 2H), 3.75-3.84 (m, 1H), 3.87 (s, 9H), 3.90 (s, 3H), 3.96 (s, 6H), 4.56 (s, 2H), 6.65-6.72 (m, 4H), 7.03 (d, 2H, J=8.8 Hz), 7.18-7.24 (m, 4H), 7.33-7.43 (m, 3H), 7.59 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).

109		5%	1.72-1.90 (m, 4H), 2.12-2.21 (m, 2H), 2.94-3.03 (m, 2H), 3.59 (s, 2H), 3.73-3.86 (m, 1H), 3.87 (s, 9H), 3.90 (s, 3H), 3.93 (s, 6H), 4.54 (s, 2H), 6.66-6.70 (m, 4H), 6.75 (s, 2H), 7.03 (d, 2H, J=9.0 Hz), 7.21 (d, 1H, J=7.2 Hz), 7.32-7.41 (m, 3H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.6 Hz), 8.69 (d, 1H, J=1.6 Hz).
110		62%	1.72-1.89 (m, 4H), 2.08-2.20 (m, 2H), 2.97-3.07 (m, 2H), 3.59 (s, 2H), 3.73-3.83 (m, 1H), 3.87 (s, 9H), 3.89 (s, 3H), 3.92 (s, 6H), 4.55 (s, 2H), 6.67 (d, 2H, J=9.3 Hz), 6.69 (s, 2H), 6.76 (s, 2H), 7.02 (d, 2H, J=8.6 Hz), 7.20 (d, 1H, J=7.6 Hz), 7.25-7.47 (m, 7H).

Preparation Example 139

Synthesis of 1-(tert-butoxycarbonyl)-4-[[4-(methylthio)phenyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 4-(methylthio)aniline (3.33 g) was treated in the same manner as described in Preparation Example 37 to give white powder of the title compound.

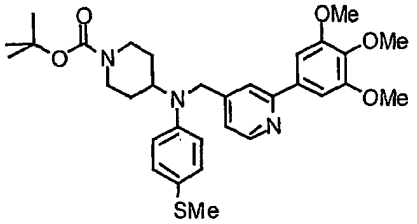
Yield: 3.80 g (49%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.26-1.38 (m, 2H), 1.46 (s, 9H), 1.98-2.06 (m, 2H), 2.41 (s, 3H), 2.88-2.97 (m, 2H), 3.36-3.45 (m, 2H), 3.48-3.56 (br, 1H), 3.96-4.12 (m, 2H), 6.55 (d, 2H, J=8.8 Hz), 7.21 (d, 2H, J=8.8 Hz).

Preparation Example 140

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(methylthio)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(methylthio)phenyl]amino]piperidine (644 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

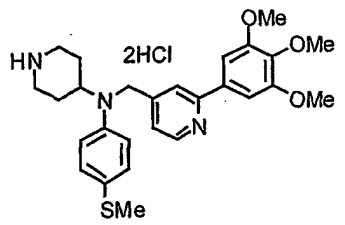
Yield: 671 mg (58%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.50-1.66 (m, 2H), 1.81-1.89 (m, 2H), 2.40 (s, 3H), 2.74-2.87 (m, 2H), 3.88-3.94 (m, 1H), 3.90 (s, 3H), 3.94 (s, 6H), 4.15-4.29 (m, 2H), 4.48 (s, 2H), 6.67 (d, 2H, J=9.0 Hz), 7.11-7.18 (m, 1H), 7.16 (s, 2H), 7.22 (d, 2H, J=6.6 Hz), 7.54 (s, 1H), 8.57 (d, 1H, J=5.1 Hz).

Preparation Example 141

Synthesis of

4-[N-[4-(methylthio)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-[4-(methylthio)phenyl]-N-[[2-(3,4,5-trimethoxy phenyl)pyridin-4-yl]methyl]amino]piperidine (671 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

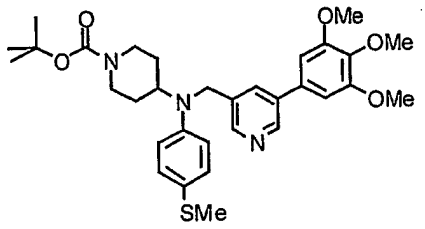
Yield: 602 mg (94%).

Preparation Example 142

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(methylthio)phenyl]-N-[[3-(3,4,5-trimethoxyphenyl)py

ridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(methylthio)phenyl]amino]piperidine (645 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

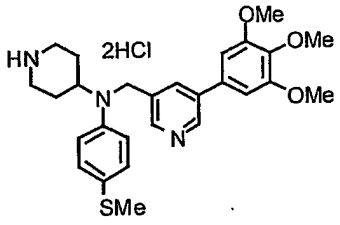
Yield: 312 mg (27%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.53-1.63 (m, 2H), 1.83-1.89 (m, 2H), 2.40 (s, 3H), 2.73-2.85 (m, 2H), 3.87-3.91 (m, 1H), 3.88 (s, 3H), 3.90 (s, 6H), 4.16-4.30 (m, 2H), 4.50 (s, 2H), 6.67 (s, 2H), 6.71 (d, 2H, J=9.0 Hz), 7.21 (d, 2H, J=9.0 Hz), 7.64 (s, 1H), 8.48 (d, 1H, J=2.2 Hz), 8.66 (d, 1H, J=2.1 Hz).

Preparation Example 143

Synthesis of

4-[N-[4-(methylthio)phenyl]-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



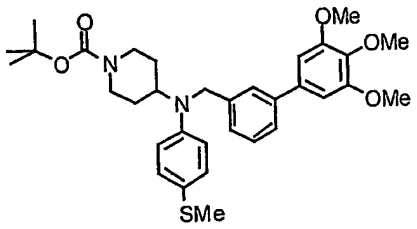
1-(tert-Butoxycarbonyl)-4-[N-[4-(methylthio)phenyl]-N-[[3-(3,4,5-trimethoxy phenyl)pyridin-5-yl]methyl]amino]piperidine (312 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 251 mg (84%).

Preparation Example 144

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(methylthio)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)ben zyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(methylthio)phenyl]amino]piperidine (645 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

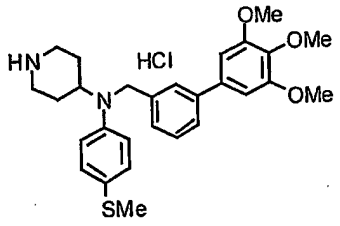
Yield: 1.10 g (95%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.55-1.68 (m, 2H), 1.81-1.90 (m, 2H), 2.39 (s, 3H), 2.73-2.86 (m, 2H), 3.87-3.91 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.15-4.29(m, 2H), 4.50 (s, 2H), 6.68-6.73 (m, 4H), 7.19-7.24 (m, 3H), 7.33-7.43 (m, 3H).

Preparation Example 145

Synthesis of

4-[N-[4-(methylthio)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:



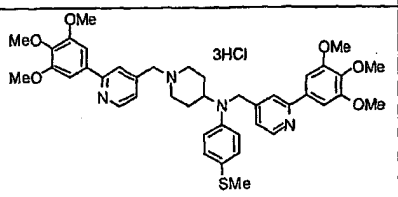
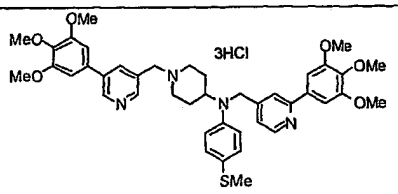
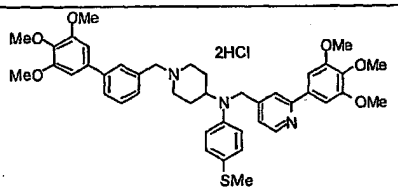
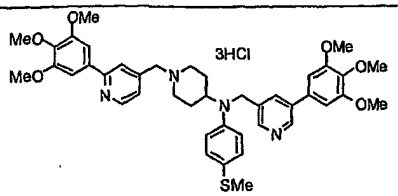
1-(tert-Butoxycarbonyl)-4-[N-[4-(methylthio)phenyl]-N-[3-(3,4,5-trimethoxyp henyl)benzyl]amino]piperidine (1.10 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

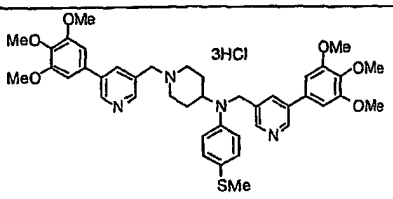
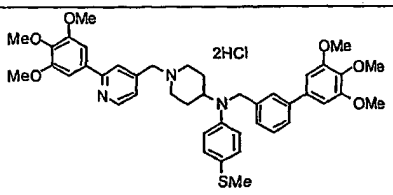
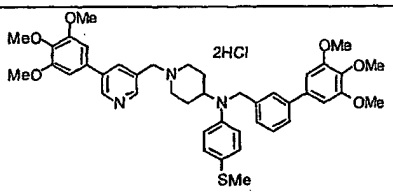
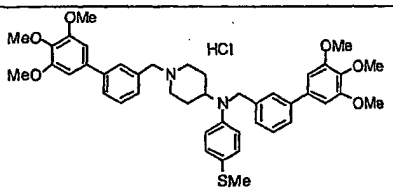
Yield: 866 mg (89%).

Examples 111 to 118

These compounds were obtained by the condensation of amines obtained in Preparation Examples 141, 143 and 145 with chloride derivatives obtained in

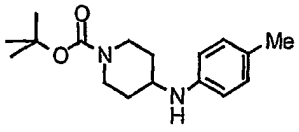
Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
111		40%	1.70-1.90 (m, 4H), 2.14-2.26 (m, 2H), 2.40 (s, 3H), 2.94-3.04 (m, 2H), 3.58 (s, 2H), 3.76-3.88 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.53 (s, 2H), 6.66 (d, 2H, J=9.0 Hz), 7.11-7.24 (m, 8H), 7.54 (s, 1H), 7.59 (s, 1H), 8.56 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=5.1 Hz).
112		53%	1.66-1.90 (m, 4H), 2.12-2.24 (m, 2H), 2.40 (s, 3H), 2.94-3.05 (m, 2H), 3.59 (s, 2H), 3.73-3.88 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.51 (s, 2H), 6.65 (d, 2H, J=8.8 Hz), 6.75 (s, 2H), 7.12 (d, 1H, J=4.9 Hz), 7.14 (s, 2H), 7.21 (d, 2H, J=8.8 Hz), 7.53 (s, 1H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.9 Hz), 6.55 (d, 1H, J=4.9 Hz), 8.69 (d, 1H, J=1.4 Hz).
113		53%	1.68-1.89 (m, 4H), 2.10-2.20 (m, 2H), 2.39 (s, 3H), 2.98-3.07 (m, 2H), 3.58 (s, 2H), 3.75-3.87 (m, 1H), 3.89 (s, 6H), 3.92 (s, 6H), 3.92 (s, 6H), 4.51 (s, 2H), 6.65 (d, 2H, J=9.0 Hz), 6.76 (s, 2H), 7.11 (d, 1H, J=5.1 Hz), 7.14 (s, 2H), 7.21 (d, 2H, J=8.8 Hz), 7.29 (d, 1H, J=7.4 Hz), 7.37 (dd, 1H, J=7.6 Hz, 7.6 Hz), 7.42-7.49 (m, 2H), 7.52 (s, 1H), 8.54 (d, 1H, J=4.9 Hz).
114		50%	1.57-2.00 (m, 4H), 2.12-2.30 (m, 2H), 2.39 (s, 3H), 2.90-3.13 (m, 2H), 3.50-3.74 (m, 2H), 3.75-3.86 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 6H), 3.97 (s, 6H), 4.57 (s, 2H), 6.66 (s, 2H), 6.70 (d, 2H, J=9.0 Hz), 7.17-7.30 (m, 5H), 7.66(br, 2H), 8.48 (s, 1H),

			8.58-8.70 (m, 2H).
115		59%	1.68-1.92 (m, 4H), 2.12-2.27 (m, 2H), 2.39 (s, 3H), 2.94-3.08 (m, 2H), 3.60 (s, 2H), 3.74-3.83 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.55 (s, 2H), 6.66 (s, 2H), 6.69 (d, 2H, J=8.8 Hz), 6.73-6.80 (m, 2H), 7.20 (d, 2H, J=8.8 Hz), 7.64 (s, 1H), 7.77(br, 1H), 8.48 (s, 1H), 8.50 (s, 1H), 8.65 (s, 1H), 8.71 (s, 1H).
116		85%	1.76-1.93 (m, 4H), 2.14-2.24 (m, 2H), 2.39 (s, 3H), 2.94-3.03 (m, 2H), 3.57 (s, 2H), 3.76-3.86 (m, 1H), 3.88 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.55 (s, 2H), 6.67-6.73 (m, 4H), 7.18-7.29 (m, 6H), 7.34 (dd, 1H, J=7.6 Hz, 7.6 Hz), 7.37-7.44 (m, 2H), 7.59 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).
117		53%	1.72-1.90 (m, 4H), 2.12-2.22 (m, 2H), 2.39 (s, 3H), 2.95-3.05 (m, 2H), 3.59 (s, 2H), 3.74-3.85 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.93 (s, 6H), 4.54 (s, 2H), 6.67-6.70 (m, 4H), 6.75 (s, 2H), 7.19-7.23 (m, 3H), 7.33 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.36-7.40 (m, 2H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.69 (s, 1H).
118		83%	1.72-1.90 (m, 4H), 2.09-2.20 (m, 2H), 2.38 (s, 3H), 2.97-3.06 (m, 2H), 3.58 (s, 2H), 3.73-3.84 (m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.92 (s, 6H), 4.54 (s, 2H), 6.66-6.71 (m, 4H), 6.76 (s, 2H), 7.18-7.24 (m, 3H), 7.26-7.48 (m, 7H).

Preparation Example 146

Synthesis of 1-(tert-butoxycarbonyl)-4-[(4-methylphenyl)amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and *p*-toluidine (2.56 g) was treated in the same manner as described in Preparation Example 37 to give white powder of the title compound.

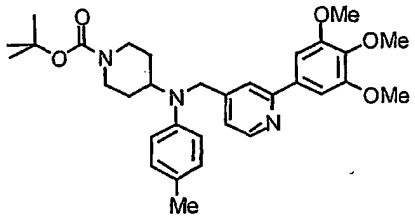
Yield: 5.79 g (83%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25-1.36 (m, 2H), 1.46 (s, 9H), 1.99-2.06 (m, 2H), 2.23 (s, 3H), 2.86-2.96 (m, 2H), 3.30-3.43 (m, 2H), 3.96-4.10 (m, 2H), 6.53 (d, 2H, J=8.4 Hz), 6.98 (d, 2H, J=8.0 Hz).

Preparation Example 147

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-methylphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-methylphenyl)amino]piperidine (581 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

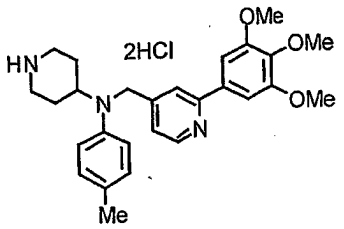
Yield: 1.00 g (91%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.55-1.59 (m, 2H), 1.81-1.90 (m, 2H), 2.23 (s, 3H), 2.72-2.86 (m, 2H), 3.81-3.94 (m, 1H), 3.89 (s, 3H), 3.93 (s, 6H), 4.14-4.30 (m, 2H), 4.45 (s, 2H), 6.66 (d, 2H, J=8.6 Hz), 7.02 (d, 2H, J=8.2 Hz), 7.13-7.16 (m, 3H), 7.55 (s, 1H), 8.55 (d, 1H, J=8.1 Hz).

Preparation Example 148

Synthesis of

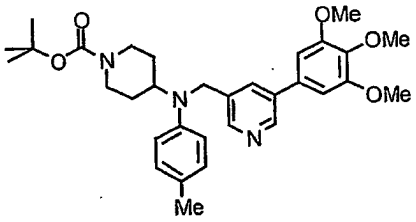
4-[N-(4-methylphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-methylphenyl)-N-[[2-(3,4,5-trimethoxypheny l)pyridin-4-yl]methyl]amino]piperidine (1.00 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 924 mg (97%).

Preparation Example 149

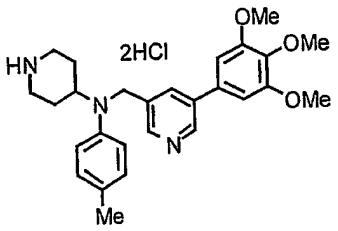
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-methylphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-methylphenyl)amino]piperidine (581 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 426 mg (39%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.52-1.70 (m, 2H), 1.82-1.90 (m, 2H), 2.23 (s, 3H), 2.72-2.86 (m, 2H), 3.77-3.86 (m, 1H), 3.88 (s, 3H), 3.90 (s, 6H), 4.10-4.28 (m, 2H), 4.47 (s, 2H), 6.67 (s, 2H), 6.70 (d, 2H, J=8.6 Hz), 7.01 (d, 2H, J=8.2 Hz), 7.67 (dd, 1H, J=2.1 Hz, 2.1 Hz), 8.50 (d, 1H, J=2.0 Hz), 8.64 (d, 1H, J=2.2 Hz).

Preparation Example 150

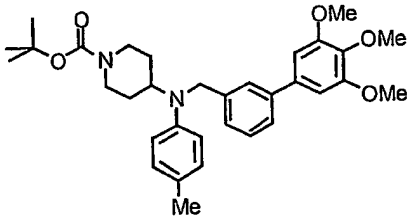
Synthesis of
4-[N-(4-methylphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-methylphenyl)-N-[[3-(3,4,5-trimethoxypheny l)pyridin-5-yl]methyl]amino]piperidine (426 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 400 mg (99%).

Preparation Example 151

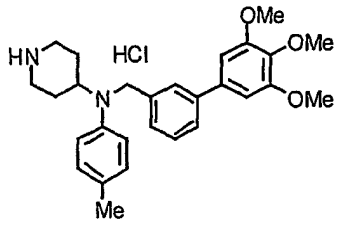
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-methylphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]a mino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-methylphenyl)amino]piperidine (581 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 1.03 g (94%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H), 1.50-1.66 (m, 2H), 1.83-1.90 (m, 2H), 2.23 (s, 3H), 2.72-2.85 (m, 2H), 3.82-3.92 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.11-4.30 (m, 2H), 4.47 (s, 2H), 6.68 (d, 2H, J=8.6 Hz), 6.71 (s, 2H), 7.00 (d, 2H, J=8.8 Hz), 7.23-7.27 (m, 1H), 7.32-7.44 (m, 3H).

Preparation Example 152

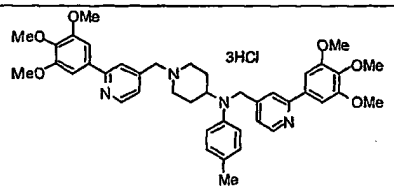
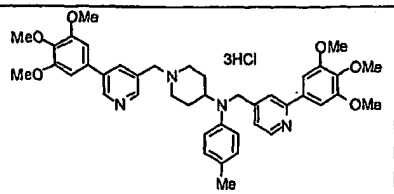
Synthesis of
4-[N-(4-methylphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

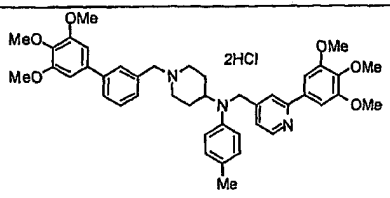
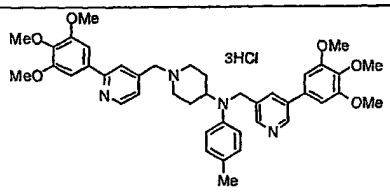
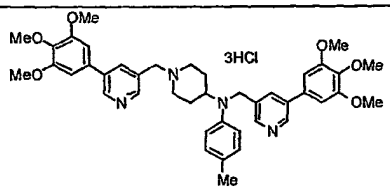
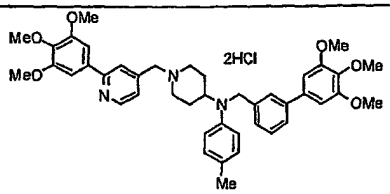


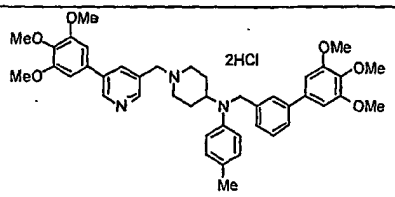
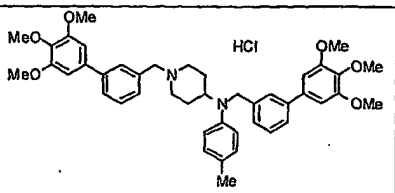
1-(tert-Butoxycarbonyl)-4-[N-(4-methylphenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (1.03 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 882 mg (97%).

Examples 119 to 126

These compounds were obtained by the condensation of amines obtained in Preparation Examples148, 150 and 152 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

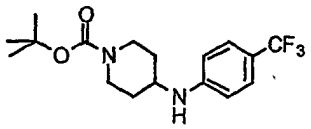
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
119		66%	1.70-1.82 (m, 2H), 1.83-1.91 (m, 2H), 2.13-2.25 (m, 2H), 2.23 (s, 3H), 2.96-3.02 (m, 2H), 3.57 (s, 2H), 3.73-3.83 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.50 (s, 2H), 6.64 (d, 2H, J=8.8 Hz), 7.01 (d, 2H, J=8.5 Hz), 7.13-7.17 (m, 3H), 7.20 (d, 1H, J=4.9 Hz), 7.22 (s, 2H), 7.56 (s, 1H), 7.59 (s, 1H), 8.54 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=4.9 Hz).
120		41%	1.60-1.91 (m, 4H), 2.12-2.24 (m, 2H), 2.23 (s, 3H), 2.95-3.05 (m, 2H), 3.59 (s, 2H), 3.73-3.83 (m, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.49 (s, 2H), 6.63 (d, 2H, J=8.6 Hz), 6.75 (s, 2H), 7.00 (d, 2H, J=8.6 Hz), 7.13-7.16 (m, 3H), 7.55 (s,

			1H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.53 (d, 1H, J=5.1 Hz), 8.70 (s, 1H).
121		69%	1.67-1.80 (m, 2H), 1.81-1.89 (m, 2H), 2.09-2.20 (m, 2H), 2.22 (s, 3H), 2.98-3.06 (m, 2H), 3.58 (s, 2H), 3.72-3.81 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 3.92 (s, 6H), 4.49 (s, 2H), 6.63 (d, 2H, J=8.4 Hz), 6.76 (s, 2H), 7.00 (d, 2H, J=8.6 Hz), 7.12-7.15 (m, 3H), 7.26-7.32 (m, 1H), 7.37 (dd, 1H, J=7.6 Hz, 7.6 Hz), 7.41-7.48 (m, 2H), 7.55 (s, 1H), 8.53 (d, 1H, J=5.0 Hz).
122		47%	1.55-2.00 (m, 4H), 2.12-2.31 (m, 2H), 2.22 (s, 3H), 2.93-3.10 (m, 2H), 3.60(br, 2H), 3.69-3.80 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.53 (s, 2H), 6.66 (s, 2H), 6.69 (d, 2H, J=8.6 Hz), 7.00 (d, 2H, J=8.6 Hz), 7.19-7.27 (m, 4H), 7.68 (s, 1H), 8.50 (s, 1H), 8.60 (d, 1H, J=4.9 Hz), 8.64 (d, 1H, J=2.2 Hz).
123		34%	1.67-1.98 (m, 4H), 2.10-2.38 (m, 2H), 2.22 (s, 3H), 2.85-3.10 (m, 2H), 3.53-3.67 (s, 2H), 3.67-3.79 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.51 (s, 2H), 6.66 (s, 2H), 6.68 (d, 2H, J=8.8 Hz), 6.76 (s, 2H), 7.00 (d, 2H, J=8.2 Hz), 7.67 (s, 1H), 7.77(br, 1H), 8.47-8.53 (m, 2H), 8.63 (d, 1H, J=2.0 Hz), 8.70 (s, 1H).
124		91%	1.73-1.92 (m, 4H), 2.12-2.26 (m, 2H), 2.21 (s, 3H), 2.92-3.02 (m, 2H), 3.57 (s, 2H), 3.72-3.82 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.95 (s, 6H), 4.53 (s, 2H), 6.67 (d, 2H, J=7.8 Hz), 6.70 (s, 2H), 6.99 (d, 2H, J=8.0 Hz), 7.18-7.25 (m, 4H), 7.33 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.38 (d, 1H, J=7.2 Hz), 7.42 (s, 1H),

			7.59 (s, 1H), 8.58 (d, 1H, J=4.7 Hz).
125		74%	1.70-1.92 (m, 4H), 2.10-2.28 (m, 2H), 2.21 (s, 3H), 2.92-3.06 (m, 2H), 3.58 (s, 2H), 3.72-3.82 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.93 (s, 6H), 4.51 (s, 2H), 6.66 (d, 2H, J=8.6 Hz), 6.70 (s, 2H), 6.75 (s, 2H), 7.23 (d, 1H, J=7.0 Hz), 7.32 (dd, 1H, J=7.6 Hz, 7.6 Hz), 7.37 (d, 1H, J=7.8 Hz), 7.41 (s, 1H), 7.77 (s, 1H), 8.49 (s, 1H), 8.69 (s, 1H).
126		84%	1.71-1.88 (m, 4H), 2.08-2.18 (m, 2H), 2.21 (s, 3H), 2.96-3.04 (m, 2H), 3.58 (s, 2H), 3.71-3.83 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 6H), 4.52 (s, 2H), 6.66 (d, 2H, J=8.6 Hz), 6.70 (s, 2H), 6.76 (s, 2H), 6.98 (d, 2H, J=8.3 Hz), 7.22-7.47 (m, 8H).

Preparation Example 153

Synthesis of 1-(tert-butoxycarbonyl)-4-[[4-(trifluoromethyl)phenyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 4-(trifluoromethyl)aniline (3.85 g) was treated in the same manner as described in Preparation Example 37 to give white powder of the title compound.

Yield: 3.30 g (40%).

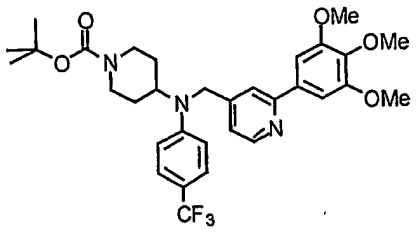
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30-1.41 (m, 2H), 1.47 (s, 9H), 2.00-2.07 (m, 2H), 2.88-2.99 (m, 2H), 3.32-3.52 (m, 1H), 3.83-3.89 (m, 1H), 4.00-4.14 (m, 2H), 6.59 (d, 2H, J=8.4 Hz), 7.39 (d, 2H, J=8.4Hz).

Preparation Example 154

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(trifluoromethyl)phenyl]-N-[[2-(3,4,5-trimethoxypheny

l)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[[4-(trifluoromethyl)phenyl]amino]piperidine (688 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

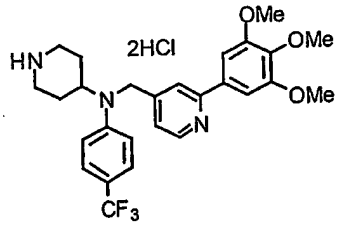
Yield: 412 mg (34%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.54-1.68 (m, 2H), 1.81-1.90 (m, 2H), 2.77-2.90 (m, 2H), 3.89 (s, 3H), 3.92 (s, 6H), 3.98-4.07 (m, 1H), 4.18-4.33 (m, 2H), 4.55 (s, 2H), 6.73 (d, 2H, J=8.8 Hz), 7.09 (d, 1H, J=3.7 Hz), 7.13 (s, 2H), 7.44 (d, 2H, J=8.8 Hz), 7.49 (s, 1H), 8.58 (d, 1H, J=5.1 Hz).

Preparation Example 155

Synthesis of

4-[N-[4-(trifluoromethyl)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



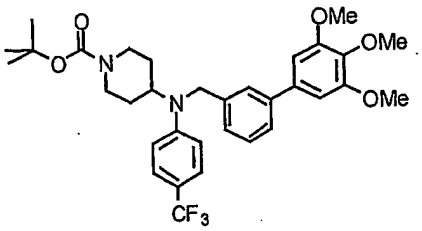
1-(tert-Butoxycarbonyl)-4-[N-[4-(trifluoromethyl)phenyl]-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (412 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 359 mg (91%).

Preparation Example 156

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[4-(trifluoromethyl)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



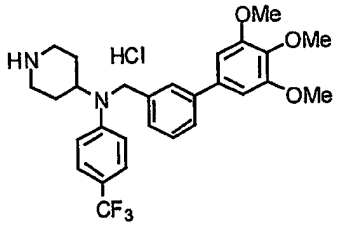
1-(tert-Butoxycarbonyl)-4-[[4-(trifluoromethyl)phenyl]amino]piperidine (689 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

Yield: 522 mg (44%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.58-1.70 (m, 2H), 1.83-1.90 (m, 2H), 2.76-2.87 (m, 2H), 3.87 (s, 6H), 3.88 (s, 3H), 3.96-4.06 (m, 1H), 4.15-4.30 (m, 2H), 4.58 (s, 2H), 6.68 (s, 2H), 6.76 (d, 2H, J=8.8 Hz), 7.19 (s, 1H, J=7.4 Hz), 7.33-7.44 (m, 5H).

Preparation Example 157

Synthesis of 4-[N-[4-(trifluoromethyl)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidin e hydrochloride:



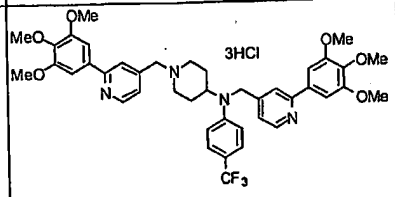
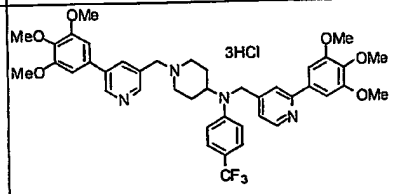
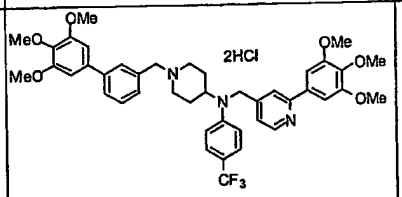
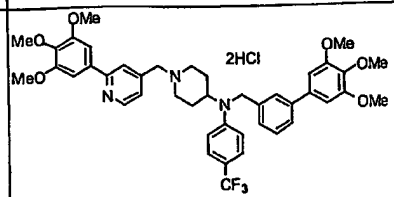
1-(tert-Butoxycarbonyl)-4-[N-[4-(trifluoromethyl)phenyl]-N-[3-(3,4,5-trimeth oxyphenyl)benzyl]amino]piperidine (522 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

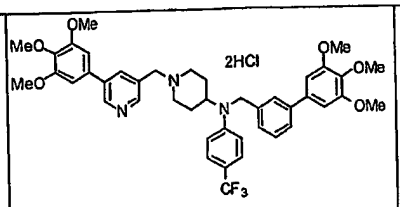
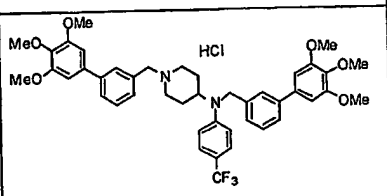
Yield: 460 mg (99%).

Example 127 to 132

These compounds were obtained by the condensation of amines obtained in

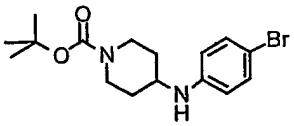
Preparation Examples 155 and 157 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
127		72%	1.74-1.92 (m, 4H), 2.17-2.26 (m, 2H), 2.96-3.04 (m, 2H), 3.59 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.96 (s, 6H), 4.60 (s, 2H), 6.72 (d, 2H, J=8.8 Hz), 7.10 (d, 1H, J=4.9 Hz), 7.13 (s, 2H), 7.20 (d, 1H, J=5.1 Hz), 7.43 (d, 2H, J=8.8 Hz), 7.50 (s, 1H), 7.59 (s, 1H), 8.56 (d, 1H, J=4.9 Hz), 8.58 (d, 1H, J=5.1 Hz).
128		51%	1.70-1.90 (m, 4H), 2.14-2.28 (m, 2H), 2.96-3.08 (m, 2H), 3.61 (s, 2H), 3.87-3.96 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.91 (s, 6H), 3.93 (s, 6H), 4.59 (s, 2H), 6.71 (d, 2H, J=8.8 Hz), 6.75 (s, 2H), 7.07-7.15 (m, 3H), 7.43 (d, 2H, J=8.8 Hz), 7.49 (s, 1H), 7.76 (s, 1H), 8.51 (d, 1H, J=1.8 Hz), 8.57 (d, 1H, J=5.1 Hz), 8.70 (s, 1H).
129		59%	1.72-1.88 (m, 4H), 2.11-2.24 (m, 2H), 2.98-3.10 (m, 2H), 3.59 (s, 2H), 3.87-3.95 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 6H), 3.92 (s, 6H), 4.59 (s, 2H), 6.71 (d, 2H, J=9.0 Hz), 6.76 (s, 2H), 7.08 (d, 1H, J=5.1 Hz), 7.12 (s, 2H), 7.29 (d, 1H, J=7.4 Hz), 7.37 (dd, 1H, J=7.6 Hz, 7.6 Hz), 7.40-7.52 (m, 5H), 8.56 (d, 1H, J=5.1 Hz).
130		81%	1.78-1.94 (m, 4H), 2.15-2.27 (m, 2H), 2.94-3.08 (m, 2H), 3.58 (s, 2H), 3.86 (s, 6H), 3.87 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.63 (s, 2H), 6.67 (s, 2H), 6.74 (d, 2H, J=8.8 Hz), 7.17-7.24 (m, 4H), 7.34-7.45 (m, 5H), 7.59 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

131		54%	1.75-1.90 (m, 4H), 2.14-2.24 (m, 2H), 2.95-3.04 (m, 2H), 3.60 (s, 2H), 3.84-3.88 (m, 1H), 3.86 (m, 1H), 3.87 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 4.61 (s, 2H), 6.67 (s, 2H), 6.72-6.77 (m, 4H), 7.18 (d, 1H, J=7.4 Hz), 7.33-7.43 (m, 5H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.9 Hz), 8.69 (d, 1H, J=1.9 Hz).
132		67%	1.76-1.88 (m, 4H), 2.11-2.19 (m, 2H), 2.98-3.06 (m, 2H), 3.59 (s, 2H), 3.86 (s, 6H), 3.87 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 4.61 (s, 2H), 6.67 (s, 2H), 6.73 (d, 2H, J=8.8 Hz), 6.76 (s, 2H), 7.18 (d, 1H, J=7.3 Hz), 7.29 (d, 1H, J=7.6 Hz), 7.32-7.47 (m, 8H).

Preparation Example 158

Synthesis of 4-(4-bromophenyl)amino-1-(tert-butoxycarbonyl)piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 4-bromoaniline (4.11 g) was treated in the same manner as described in Example 37 to give white crystalline powder of the title compound.

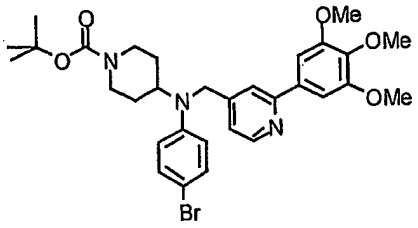
Yield: 3.09 g (36%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25-1.37 (m, 2H), 1.46 (s, 9H), 1.97-2.05 (m, 2H), 2.86-2.96 (m, 2H), 3.33-3.42 (m, 2H), 3.47-3.57 (m, 1H), 3.96-4.12 (m, 2H), 6.47 (d, 2H, J=8.8 Hz), 7.24 (d, 2H, J=9.0 Hz).

Preparation Example 159

Synthesis of

4-[N-(4-bromophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-(tert-butoxycarbonyl)piperidine:



4-(4-Bromophenyl)amino-1-(tert-butoxycarbonyl)piperidine (711 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

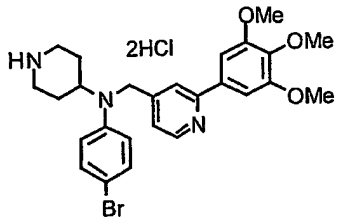
Yield: 607 mg (50%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.50-1.64 (m, 2H), 1.81-1.88 (m, 2H), 2.74-2.88 (m, 2H), 3.86-3.94 (m, 1H), 3.89 (s, 3H), 3.93 (s, 6H), 4.14-4.32 (m, 2H), 4.46 (s, 2H), 6.59 (d, 2H, J=9.1 Hz), 7.10 (d, 1H, J=5.2 Hz), 7.14 (s, 2H), 7.28 (d, 2H, J=9.1 Hz), 7.50 (s, 1H), 8.57 (d, 1H, J=5.0 Hz).

Preparation Example 160

Synthesis of

4-[N-(4-bromophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



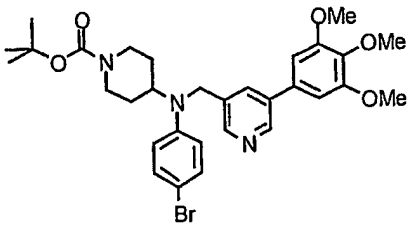
4-[N-(4-Bromophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-(tert-butoxycarbonyl)piperidine (607 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 541 mg (93%).

Preparation Example 161

Synthesis of

4-[N-(4-bromophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-(tert-butoxycarbonyl)piperidine:



4-(4-Bromophenyl)amino-1-(tert-butoxycarbonyl)piperidine (711 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

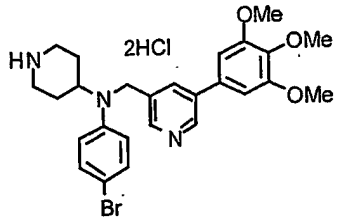
Yield: 347 mg (28%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.52-1.67 (m, 2H), 1.80-1.89 (m, 2H), 2.72-2.87 (m, 2H), 3.82-3.92 (m, 1H), 3.89 (s, 3H), 3.90 (s, 6H), 4.14-4.33 (m, 2H), 4.50 (s, 2H), 6.63 (d, 2H, J=9.2 Hz), 6.65 (s, 2H), 7.28 (d, 2H, J=9.4 Hz), 7.61 (s, 1H), 8.47 (d, 1H, J=2.0 Hz), 8.67 (d, 1H, J=2.2 Hz).

Preparation Example 162

Synthesis of

4-[N-(4-bromophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



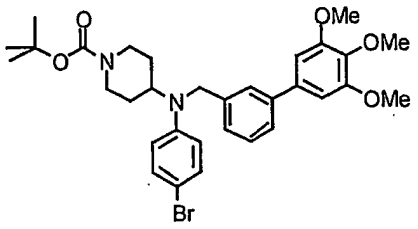
4-[N-(4-Bromophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-(tert-butoxycarbonyl)piperidine (347 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 302 mg (91%).

Preparation Example 163

Synthesis of

4-[N-(4-bromophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-(tert-butoxycarbonyl)piperidine:



4-(4-Bromophenyl)amino-1-(tert-butoxycarbonyl)piperidine (711 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

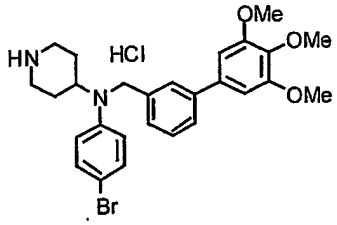
Yield: 1.14 g (93%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.52-1.67 (m, 2H), 1.80-1.89 (m, 2H), 2.72-2.86 (m, 2H), 3.84-3.91 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.11-4.32 (m, 2H), 4.49 (s, 2H), 6.62 (d, 2H, J=9.2 Hz), 6.69 (s, 2H), 7.19 (d, 1H, J=7.6 Hz), 7.25 (d, 2H, J=5.5 Hz), 7.32-7.42 (m, 3H).

Preparation Example 164

Synthesis of

4-[N-(4-bromophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:



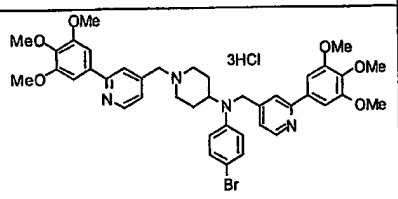
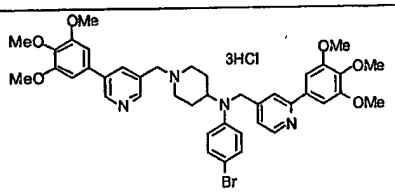
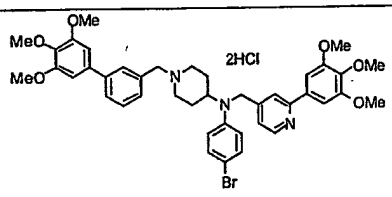
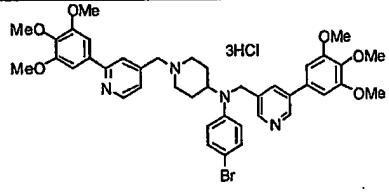
4-[N-(4-Bromophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-(tert-butoxycarbonyl)piperidine (1.14 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

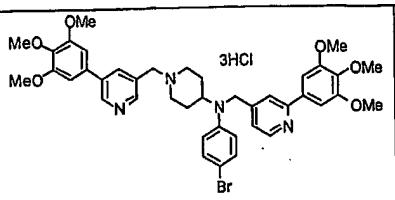
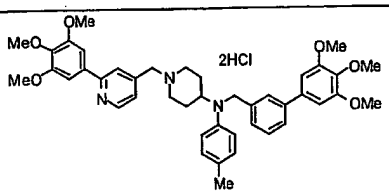
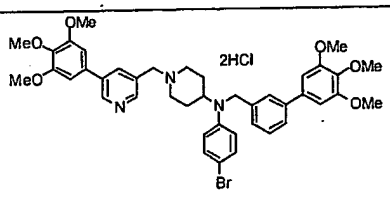
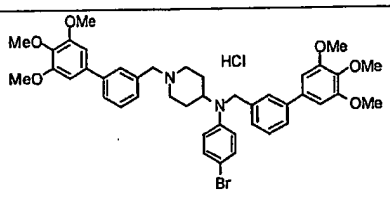
Yield: 973 mg (84%).

Examples 133 to 140

These compounds were obtained by the condensation of amines obtained in Preparation Examples 160, 162 and 164 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed

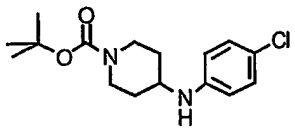
below.

Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
133		52%	1.70-1.90 (m, 4H), 2.14-2.25 (m, 2H), 2.94-3.04 (m, 2H), 3.58 (s, 2H), 3.73-3.84 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.96 (s, 6H), 4.52 (s, 2H), 6.57 (d, 2H, J=8.8 Hz), 7.10 (d, 1H, J=4.9 Hz), 7.14 (s, 2H), 7.20 (d, 1H, J=4.9 Hz), 7.22 (s, 2H), 7.26 (d, 2H, J=8.5 Hz), 7.51 (s, 1H), 7.59 (s, 1H), 8.56 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=4.9 Hz).
134		56%	1.68-1.88 (m, 4H), 2.12-2.24 (m, 2H), 2.95-3.04 (m, 2H), 3.59 (s, 2H), 3.72-3.84 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.50 (s, 2H), 6.57 (d, 2H, J=9.2 Hz), 6.74 (s, 2H), 7.09 (d, 1H, J=3.9 Hz), 7.13 (s, 2H), 7.26 (d, 2H, J=8.8 Hz), 7.50 (s, 1H), 7.75 (s, 1H), 8.50 (d, 1H, J=2.0 Hz), 8.55 (d, 1H, J=5.0 Hz), 8.69 (d, 1H, J=2.0 Hz).
135		65%	1.70-1.86 (m, 4H), 2.10-2.20 (m, 2H), 2.97-3.08 (m, 2H), 3.59 (s, 2H), 3.72-3.82 (m, 1H), 3.89 (s, 6H), 3.92 (s, 6H), 3.92 (s, 6H), 4.50 (s, 2H), 6.56 (d, 2H, J=9.2 Hz), 6.76 (s, 2H), 7.09 (d, 1H, J=5.1 Hz), 7.13 (s, 2H), 7.23-7.33 (m, 3H), 7.37 (dd, 1H, J=7.4 Hz), 7.41-7.48 (m, 2H), 7.49 (s, 1H), 8.54 (d, 1H, J=5.1 Hz).
136		49%	1.77-1.93 (m, 4H), 2.12-2.30 (m, 2H), 2.94-3.10 (m, 2H), 3.60 (s, 2H), 3.73-3.83 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.55 (s, 2H), 6.61 (d, 2H, J=9.2 Hz), 6.65 (s, 2H), 7.19-7.29 (m, 5H), 7.62(br, 2H), 8.47 (d, 1H, J=1.6 Hz), 8.60 (d, 1H, J=4.9 Hz), 8.66 (d, 1H, J=2.0 Hz).

137		50%	1.70-1.92 (m, 4H), 2.12-2.27 (m, 2H), 2.93-3.07 (m, 2H), 3.60 (s, 2H), 3.67-4.08 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.54 (s, 2H), 6.60 (d, 2H, J=9.0 Hz), 6.64 (s, 2H), 6.73-6.80 (m, 2H), 7.25 (s, 2H), 7.61 (s, 1H), 7.77(br, 1H), 8.45 (d, 1H, J=1.7 Hz), 8.50 (d, 1H, J=1.7 Hz), 8.65 (d, 1H, J=2.0 Hz).
138		81%	1.75-1.90 (m, 4H), 2.17-2.24 (m, 2H), 2.94-3.02 (m, 2H), 3.57 (s, 2H), 3.72-3.83 (m, 1H), 3.88 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.95 (s, 6H), 4.54 (s, 2H), 6.60 (d, 2H, J=9.2 Hz), 6.69 (s, 2H), 7.18-7.27 (m, 6H), 7.32-7.42 (m, 3H), 7.60 (s, 1H), 8.58 (d, 1H, J=4.9 Hz).
139		80%	1.72-1.90 (m, 4H), 2.13-2.21 (m, 2H), 2.94-3.05 (m, 2H), 3.59 (s, 2H), 3.72-3.82 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.93 (s, 6H), 4.53 (s, 2H), 6.60 (d, 2H, J=9.0 Hz), 6.68 (s, 2H), 6.75 (s, 2H), 7.19 (d, 1H, J=7.2 Hz), 7.24 (d, 2H, J=9.0 Hz), 7.31-7.41 (m, 3H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.70 (s, 1H).
140		78%	1.72-1.88 (m, 4H), 2.08-2.18 (m, 2H), 2.97-3.06 (m, 2H), 3.58 (s, 2H), 3.71-3.82 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 6H), 4.53 (s, 2H), 6.59 (d, 2H, J=9.3 Hz), 6.68 (s, 2H), 6.76 (s, 2H), 7.18 (d, 1H, J=7.3 Hz), 7.21-7.47 (m, 9H)

Preparation Example 165

Synthesis of 1-(tert-butoxycarbonyl)-4-[(4-chlorophenyl)amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 4-chloroaniline (3.05 g)

was treated in the same manner as described in Preparation Example 37 to give white powder of the title compound.

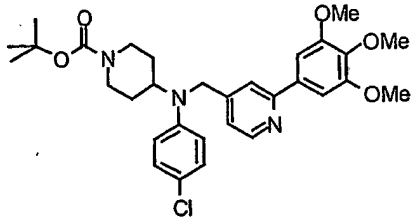
Yield: 3.80 g (49%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.24-1.38 (m, 2H), 1.46 (s, 9H), 1.97-2.05 (m, 2H), 2.86-2.96 (m, 2H), 3.32-3.42 (m, 2H), 3.51 (br, 1H), 6.52 (d, 2H, J=9.0 Hz), 7.11 (d, 2H, J=9.0 Hz).

Preparation Example 166

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-chlorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-chlorophenyl)amino]piperidine (621 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

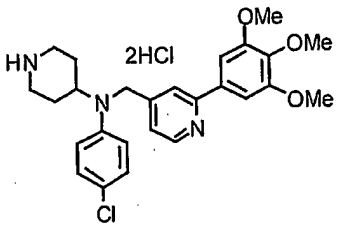
Yield: 789 mg (69%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.51-1.68 (m, 2H), 1.80-1.89 (m, 2H), 2.72-2.86 (m, 2H), 3.87-3.90 (m, 1H), 3.89 (s, 3H), 3.93 (s, 6H), 4.64 (s, 2H), 6.64 (d, 2H, J=9.0 Hz), 7.14 (d, 1H, J=5.3 Hz), 7.15 (d, 2H, J=9.0 Hz), 7.51 (s, 2H), 8.57 (d, 2H, J=5.1 Hz).

Preparation Example 167

Synthesis of

4-[N-(4-chlorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:

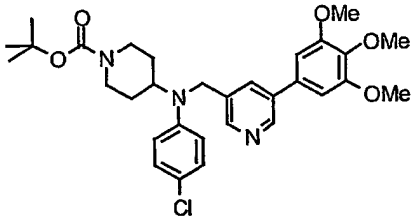


1-(tert-Butoxycarbonyl)-4-[N-(4-chlorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (789 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 673 mg (90%).

Preparation Example 168

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-chlorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:

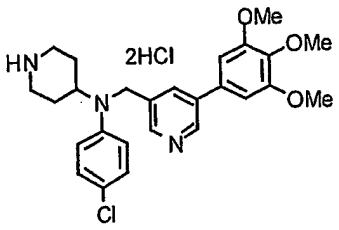


1-(tert-Butoxycarbonyl)-4-[(4-chlorophenyl)amino]piperidine (621 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 268 mg (24%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.56-1.76 (m, 2H), 1.80-1.90 (m, 2H), 2.76-2.83 (m, 2H), 3.86-3.90 (m, 1H), 3.89 (s, 3H), 3.90 (s, 6H), 4.15-4.30 (m, 2H), 4.50 (s, 2H), 6.66 (s, 2H), 6.68 (d, 2H, J=9.2 Hz), 7.15 (d, 2H, J=9.0 Hz), 7.63 (s, 1H), 8.47 (d, 1H, J=2.0 Hz), 8.66 (d, 1H, J=2.0 Hz).

Preparation Example 169

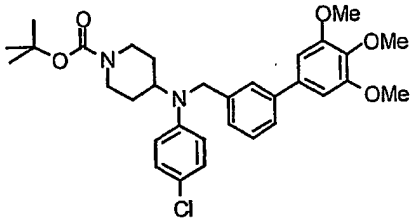
Synthesis of

4-[N-(4-chlorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



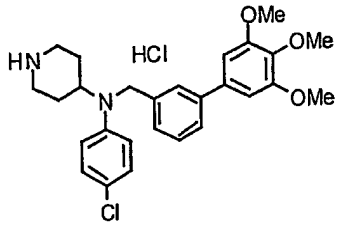
1-(tert-Butoxycarbonyl)-4-[N-(4-chlorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (268 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 233 mg (91%).

Preparation Example 170
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-chlorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[4-(chlorophenyl)amino]piperidine (622 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 1.04 g (92%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (s, 9H), 1.58-1.67 (m, 2H), 1.82-1.91 (m, 2H), 2.74-2.86 (m, 2H), 3.85-3.92 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.35-4.31 (m, 2H), 4.49 (s, 2H), 6.66 (d, 2H, J=9.2 Hz), 6.70 (s, 2H), 7.12 (d, 2H, J=9.0 Hz), 7.20 (d, 2H, J=7.3 Hz), 7.33-7.43 (m, 3H).

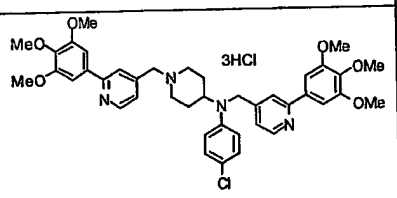
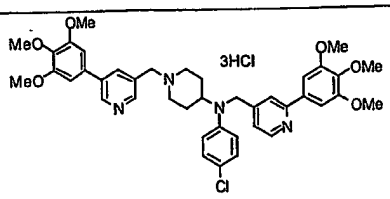
Preparation Example 171
Synthesis of
4-[N-(4-chlorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

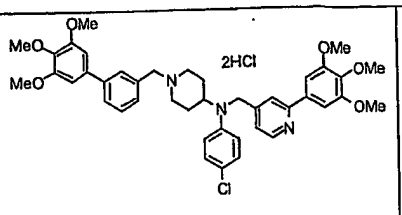
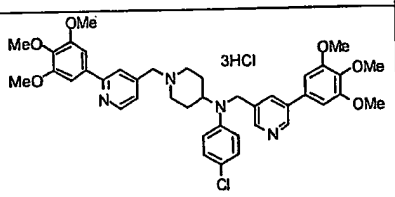
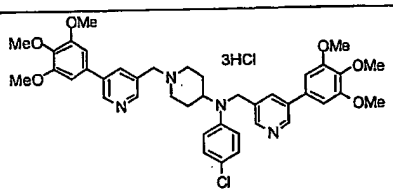
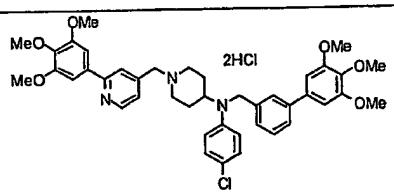
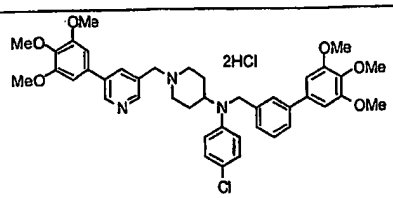


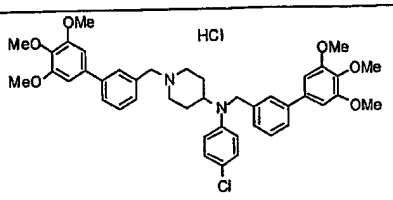
1-(tert-Butoxycarbonyl)-4-[N-(4-chlorophenyl)-N-[3-(3,4,5-trimethoxyphenyl) benzyl]amino]piperidine (1.04 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 899 mg (97%).

Example 141 to 148

These compounds were obtained by the condensation of amines obtained in Preparation Examples 167, 169 and 171 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

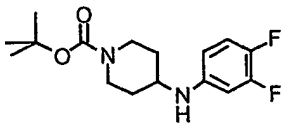
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
141		66%	1.71-1.90 (m, 4H), 2.15-2.24 (m, 2H), 2.95-3.05 (m, 2H), 3.58 (s, 2H), 3.73-3.84 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.52 (s, 2H), 6.62 (d, 2H, J=9.0 Hz), 7.10-7.16 (m, 5H), 7.19-7.24 (m, 3H), 7.52 (s, 1H), 7.59 (s, 1H), 8.56 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=4.9 Hz).
142		67%	1.69-1.90 (m, 1H), 2.12-2.25 (m, 2H), 2.93-3.06 (m, 2H), 3.59 (s, 2H), 3.72-3.83 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.50 (s, 2H), 6.62 (d, 2H, J=9.2 Hz), 6.75 (s, 2H), 7.10 (d, 1H, J=5.3 Hz), 7.13 (s, 2H), 7.13 (d, 2H, J=9.0 Hz), 7.50 (s, 1H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.55 (d, 1H, J=5.1 Hz), 8.70 (d, 1H, J=1.8 Hz).

143		70%	1.65-1.88 (m, 4H), 2.08-2.20 (m, 2H), 2.97-3.07 (m, 2H), 3.59 (s, 2H), 3.71-3.82 (m, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90-3.93 (m, 3H), 4.50 (s, 2H), 6.61 (d, 2H, J=8.2 Hz), 6.76 (s, 2H), 7.07-7.14 (m, 5H), 7.28 (d, 1H, J=6.6 Hz), 7.37 (dd, 1H, J=7.4 Hz), 7.40-7.47 (m, 2H), 7.50 (s, 1H), 8.54 (d, 1H, J=5.1 Hz).
144		57%	1.56-1.93 (m, 4H), 2.12-2.30 (m, 2H), 2.92-3.10 (m, 2H), 3.53-3.68 (m, 2H), 3.70-3.82 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.56 (s, 2H), 6.64-6.70 (m, 4H), 7.13 (d, 2H, J=9.0 Hz), 7.20-7.30 (m, 3H), 7.63(br, 2H), 8.48 (s, 1H), 8.60 (d, 1H, J=5.1 Hz), 8.66 (d, 1H, J=2.2 Hz).
145		70%	1.71-1.92 (m, 4H), 2.12-2.27 (m, 2H), 2.94-3.07 (m, 2H), 3.59 (s, 2H), 3.69-3.81 (s, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.54 (s, 2H), 6.63-6.68 (m, 4H), 6.75 (s, 2H), 7.13 (d, 2H, J=9.0 Hz), 7.62 (s, 1H), 7.76 (s, 1H), 8.47 (d, 1H, J=1.8 Hz), 8.50 (d, 1H, J=1.8 Hz), 8.65 (d, 1H, J=2.0 Hz), 8.70 (s, 1H).
146		78%	1.75-1.91 (m, 4H), 2.13-2.23 (m, 2H), 2.94-3.02 (m, 2H), 3.57 (s, 2H), 3.73-3.82 (m, 1H), 3.88 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.55 (s, 2H), 6.65 (d, 2H, J=9.0 Hz), 6.68 (s, 2H), 7.11 (d, 2H, J=8.5 Hz), 7.18-7.24 (m, 4H), 7.32-7.42 (m, 3H), 7.59 (s, 1H), 8.59 (d, 1H, J=4.9 Hz).
147		63%	1.72-1.89 (m, 4H), 2.12-2.21 (m, 2H), 2.94-3.03 (m, 2H), 3.59 (s, 2H), 3.72-3.82 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.53 (s, 2H), 6.64 (d, 2H, J=9.2 Hz), 6.68 (s, 2H), 6.75 (s, 2H), 7.11 (d, 2H), 7.19 (d, 1H,

			J=7.6 Hz), 7.32-7.40 (m, 3H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.69 (d, 1H, J=2.2 Hz).
148		68%	1.72-1.87 (m, 4H), 2.08-2.18 (m, 2H), 2.97-3.05 (m, 2H), 3.58 (s, 2H), 3.71-3.82 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 6H), 4.53 (s, 2H), 6.64 (dt, 2H, J=9.3 Hz, 2.9 Hz), 6.68 (s, 2H), 6.76 (s, 2H), 7.10 (dt, 2H, J=9.0 Hz, 2.8 Hz), 7.19 (d, 1H, J=7.6 Hz), 7.24-7.47 (m, 7H).

Preparation Example 172

Synthesis of 1-(tert-butoxycarbonyl)-4-[(3,4-difluorophenyl)amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 3,4-difluoroaniline (3.09 g) was treated in the same manner as described in Preparation Example 37 to give light brown prism crystal of the title compound.

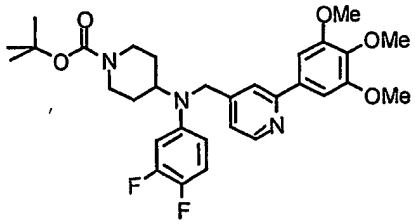
Yield: 4.66 g (62%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.24-1.37 (m, 2H), 1.46 (s, 9H), 1.97-2.05 (m, 2H), 2.85-2.96 (m, 2H), 3.26-3.36 (m, 1H), 3.38-3.52 (m, 1H), 3.96-4.14 (m, 2H), 6.22-6.28 (m, 1H), 6.38 (ddd, 1H, J=12.7 Hz, 6.6 Hz, 2.9 Hz), 6.94 (dd, 1H, J=19.1 Hz, 9.0 Hz).

Preparation Example 173

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(3,4-difluorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(3,4-difluorophenyl)amino]piperidine (625 mg)

and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

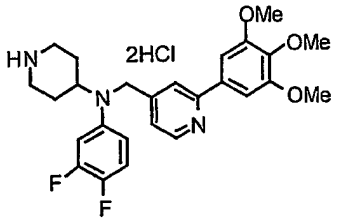
Yield: 534 mg (47%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.50-1.70 (m, 2H), 1.82-1.90 (m, 2H), 2.73-2.88 (m, 2H), 3.90 (s, 3H), 3.94 (s, 6H), 4.15-4.30 (m, 2H), 4.43 (s, 2H), 6.33-6.39 (m, 1H), 6.52 (ddd, 1H, J=13.6 Hz, 6.4 Hz, 3.1 Hz), 6.98 (dd, 1H, J=19.1 Hz, 9.2 Hz), 7.11 (dd, 1H, J=5.0 Hz, 1.3 Hz), 7.16 (s, 2H), 7.51 (s, 1H), 8.58 (d, 1H, J=5.1 Hz).

Preparation Example 174

Synthesis of

4-[N-(3,4-difluorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



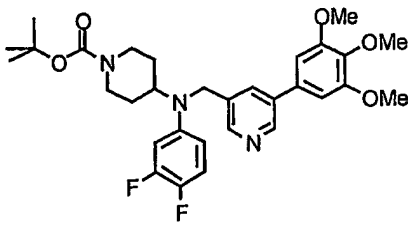
1-(tert-Butoxycarbonyl)-4-[N-(3,4-difluorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (534 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 442 mg (87%).

Preparation Example 175

Synthesis of

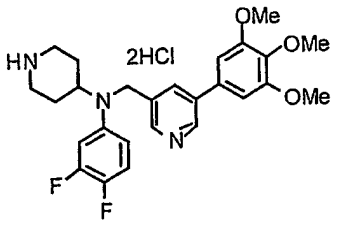
1-(tert-butoxycarbonyl)-4-[N-(3,4-difluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(3,4-difluorophenyl)amino]piperidine (625 mg)

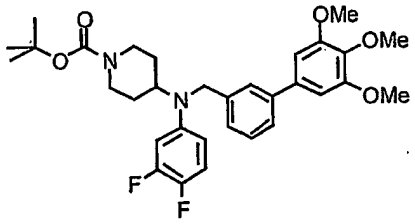
and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 350 mg (31%).

Preparation Example176
Synthesis of
4-[N-(3,4-difluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(3,4-difluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (350 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 305 mg (92%).

Preparation Example 177
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(3,4-difluorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



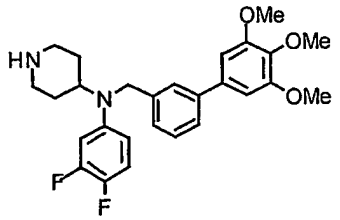
1-(tert-Butoxycarbonyl)-4-[(3,4-difluorophenyl)amino]piperidine (625 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 980 mg (86%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.52-1.66 (m, 2H), 1.81-1.89 (m, 2H), 2.72-2.85 (m, 2H), 3.78 (tt, 1H, J=11.8 Hz, 3.8 Hz), 3.88 (s, 3H), 3.90 (s, 6H), 4.12-4.30 (m, 2H), 4.45 (s, 2H), 6.36-6.42 (m, 1H), 6.54 (ddd, 1H, J=13.9 Hz, 6.8 Hz, 2.9 Hz), 6.71 (s, 2H), 6.95 (dd, 1H, J=19.2 Hz, 9.2 Hz), 7.20 (d, 1H, J=7.4 Hz), 7.36-7.43 (m, 3H).

Preparation Example 178

Synthesis of

4-[N-(3,4-difluorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

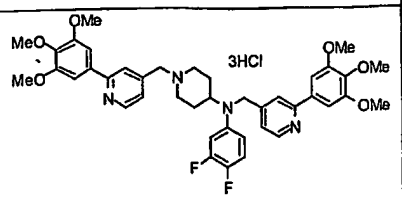


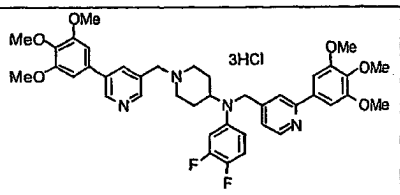
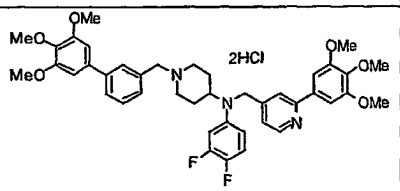
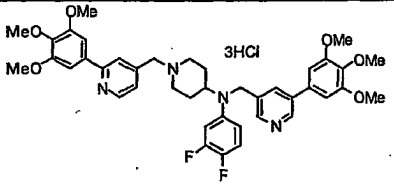
1-(tert-Butoxycarbonyl)-4-[N-(3,4-difluorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (980 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

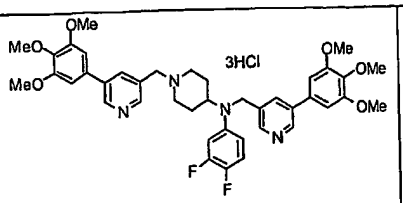
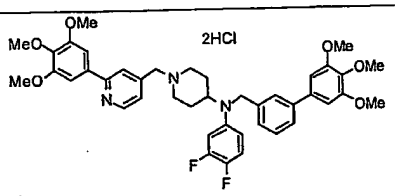
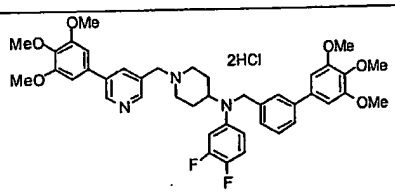
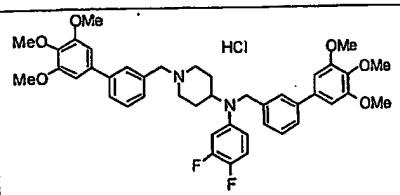
Yield: 819 mg (94%).

Example 149 to 156

These compounds were obtained by the condensation of amines obtained in Preparation Examples 174, 176 and 178 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

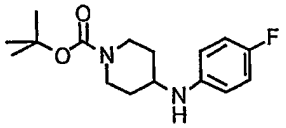
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
149		67%	1.70-1.90 (m, 4H), 2.16-2.23 (m, 2H), 2.95-3.03 (m, 2H), 3.58 (s, 2H), 3.64-3.74 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.49 (s, 2H), 6.31-6.37 (m, 1H), 6.51 (ddd, 1H,

			J=13.9 Hz, 6.6 Hz, 3.1 Hz), 6.96 (dd, 1H, J=19.2 Hz, 9.8 Hz), 7.11 (d, 1H, J=5.1 Hz), 7.15 (s, 2H), 7.20 (d, 1H, J=5.1 Hz), 7.22 (s, 2H), 7.52 (s, 1H), 7.59 (s, 1H), 8.57 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=5.1 Hz).
150		47%	1.67-1.79 (m, 2H), 1.81-1.89 (m, 2H), 2.13-2.20 (m, 2H), 2.95-3.05 (m, 2H), 3.59 (s, 2H), 3.63-3.75 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 12H), 4.47 (s, 2H), 6.30-6.36 (m, 1H), 6.50 (ddd, 1H, J=13.9 Hz, 6.6 Hz, 3.1 Hz), 6.75 (s, 2H), 6.96 (d, 1H, J=19.0 Hz, 9.4 Hz), 7.10 (d, 1H, J=4.1 Hz), 7.15 (s, 2H), 7.51 (s, 1H), 7.75 (s, 1H), 8.50 (d, 1H, J=1.8 Hz), 8.56 (d, 1H, J=5.1 Hz), 8.70 (s, 1H).
151		53%	1.68-1.87 (m, 4H), 2.09-2.18 (m, 2H), 2.98-3.06 (m, 2H), 3.58 (s, 2H), 3.63-3.72 (m, 1H), 3.89 (s, 3H), 3.89 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.47 (s, 2H), 6.33-6.35 (m, 1H), 6.50 (ddd, 1H, J=13.9 Hz, 6.4 Hz, 2.9 Hz), 6.76 (s, 2H), 6.95 (dd, 1H, J=19.2 Hz, 9.4 Hz), 7.09 (d, 1H, J=5.1 Hz), 7.15 (s, 2H), 7.25-7.30 (m, 1H), 7.37 (dd, 1H, J=7.3 Hz, 7.3 Hz), 7.42-7.46 (m, 2H), 7.50 (s, 1H), 8.56 (d, 1H, J=5.1 Hz).
152		50%	1.72-1.96 (m, 4H), 2.12-2.28 (m, 2H), 2.94-3.08 (m, 2H), 3.59 (s, 2H), 3.62-3.72 (m, 1H), 3.89 (s, 3H), 3.90 (s, 9H), 3.96 (s, 6H), 4.52 (s, 2H), 6.36-6.43 (m, 1H), 6.55 (ddd, 1H, J=13.7 Hz, 6.6 Hz, 2.9 Hz), 6.67 (s, 2H), 6.96 (dd, 1H, J=19.1 Hz, 9.2 Hz), 7.21 (dd, 1H, J=5.1 Hz, 1.2 Hz), 7.24 (s, 2H), 7.61(br, 1H), 7.64 (s, 1H), 8.47 (d, 1H, J=2.0 Hz), 8.60 (d, 1H, J=4.9 Hz), 8.67 (d, 1H, J=2.0 Hz).

153		61%	1.71-1.90 (m, 4H), 2.12-2.25 (m, 2H), 2.95-3.05 (m, 2H), 3.57-3.75 (m, 1H), 3.59 (s, 2H), 3.88 (s, 3H), 3.90 (s, 9H), 3.93 (s, 6H), 4.50 (s, 2H), 6.32-6.43 (m, 1H), 6.54 (ddd, 1H, J=13.6 Hz, 6.4 Hz, 2.7 Hz), 6.67 (s, 2H), 6.73-6.78 (m, 3H), 6.96 (dd, 1H, J=18.9 Hz, 9.6 Hz), 7.63 (s, 1H), 7.76 (s, 1H), 8.46 (s, 1H), 8.50 (d, 1H, J=1.6 Hz), 8.66 (d, 1H, J=1.8 Hz), 8.70 (d, 1H, J=2.0 Hz).
154		82%	1.74-1.90 (m, 4H), 2.13-2.22 (m, 2H), 2.95-3.01 (m, 2H), 3.57 (s, 2H), 3.63-3.73 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.51 (s, 2H), 6.34-6.40 (m, 1H), 6.52 (ddd, 1H, J=14.1 Hz, 6.6 Hz, 3.1 Hz), 6.70 (s, 2H), 6.94 (dd, 1H, J=19.2 Hz, 9.4 Hz), 7.17-7.26 (m, 4H), 7.32-7.42 (m, 3H), 7.59 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).
155		75%	1.74-1.90 (m, 4H), 2.13-2.21 (m, 2H), 2.95-3.04 (m, 2H), 3.59 (s, 2H), 3.63-3.72 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.89 (s, 3H), 3.93 (s, 6H), 4.49 (s, 2H), 6.33-6.39 (m, 1H), 6.52 (ddd, 1H, J=14.3 Hz, 3.7 Hz, 2.9 Hz), 6.69 (s, 2H), 6.75 (s, 2H), 6.94 (dd, 1H, J=19.1 Hz, 9.8 Hz), 7.19 (d, 1H, J=7.8 Hz), 7.32-7.41 (m, 3H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.5 Hz), 8.69 (s, 1H).
156		79%	1.72-1.88 (m, 4H), 2.08-2.18 (m, 2H), 2.98-3.05 (m, 2H), 3.58 (s, 2H), 3.62-3.72 (m, 1H), 3.88 (s, 3H), 3.89 (s, 9H), 3.92 (s, 6H), 4.45 (s, 2H), 6.33-6.39 (m, 1H), 6.51 (ddd, 1H, J=13.9 Hz, 6.6 Hz, 3.0 Hz), 6.69 (s, 2H), 6.76 (s, 2H), 6.93 (dd, 1H, J=19.3 Hz, 9.5 Hz), 7.19 (d, 1H, J=7.6 Hz), 7.25-7.47 (m, 7H).

Preparation Example 179

Synthesis of 1-(tert-butoxycarbonyl)-4-[(4-fluorophenyl)amino]piperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and 4-fluoroaniline (2.66 g) was treated in the same manner as described in Preparation Example 37 to give white crystalline powder of the title compound.

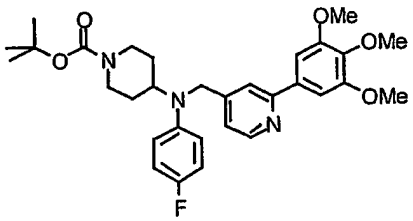
Yield: 4.99 g (71%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.23-1.36 (m, 2H), 1.46 (s, 9H), 1.97-2.05 (m, 2H), 2.84-2.96 (m, 2H), 3.30-3.39 (m, 2H), 3.96-4.14 (m, 2H), 6.51-6.57 (m, 2H), 6.84-6.91 (m, 2H).

Preparation Example 180

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-fluorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



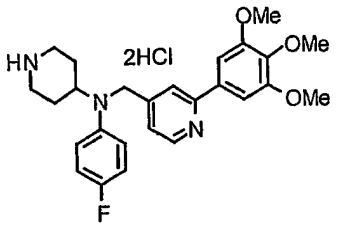
1-(tert-Butoxycarbonyl)-4-[(4-fluorophenyl)amino]piperidine (589 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

Yield: 702 mg (64%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.48-1.64 (m, 2H), 1.81-1.90 (m, 2H), 2.72-2.85 (m, 2H), 3.69-3.98 (m, 1H), 3.89 (m, 3H), 3.94 (m, 6H), 4.16-4.28 (m, 2H), 4.43 (s, 2H), 6.66-6.73 (m, 2H), 6.91 (dd, 2H, J=9.2 Hz, 9.2 Hz), 7.12-7.16 (m, 3H), 7.53 (s, 1H).

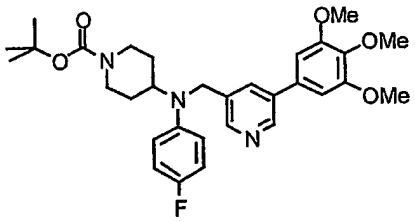
Preparation Example 181

Synthesis of
4-[N-(4-fluorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-fluorophenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (702 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 561 mg (84%).

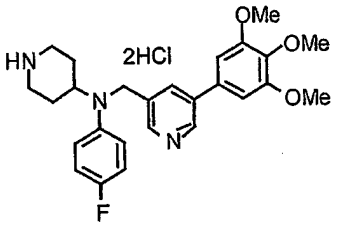
Preparation Example 182
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-fluorophenyl)amino]piperidine (589 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 190 mg (17%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.50-1.73 (m, 2H), 1.82-1.90 (m, 2H), 2.71-2.85 (m, 2H), 3.71 (tt, 1H, J=11.7 Hz, 3.1 Hz), 3.89 (s, 3H), 3.90 (s, 6H), 4.12-4.30 (m, 2H), 4.45 (s, 2H), 6.66 (s, 2H), 6.73-6.78 (m, 2H), 6.91 (dd, 2H, J=9.2 Hz, 8.2 Hz), 7.65 (s, 1H), 8.49 (d, 1H, J=2.0 Hz), 8.65 (d, 1H, J=2.0 Hz).

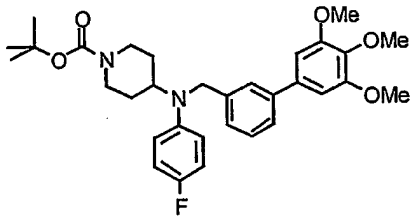
Preparation Example 183

Synthesis of
4-[N-(4-fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (190 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 165 mg (91%).

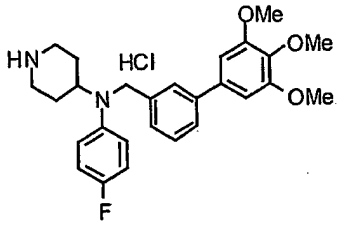
Preparation Example 184
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-fluorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-[(4-fluorophenyl)amino]piperidine (589 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 1.01 g (92%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.44 (s, 9H), 1.51-1.65 (m, 2H), 1.82-1.90 (m, 2H), 2.82-2.84 (m, 2H), 3.78 (tt, 1H, J=11.7 Hz, 3.5 Hz), 3.88 (s, 3H), 3.90 (s, 6H), 4.10-4.30 (m, 2H), 4.45 (s, 2H), 6.68-6.73 (m, 4H), 6.89 (dd, 2H, J=9.2 Hz, 8.2 Hz), 7.21-7.25 (m, 1H), 7.32-7.41 (m, 3H).

Preparation Example 185
Synthesis of

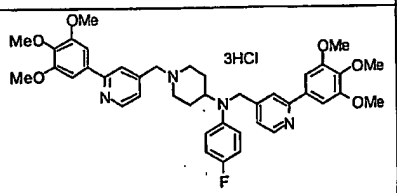
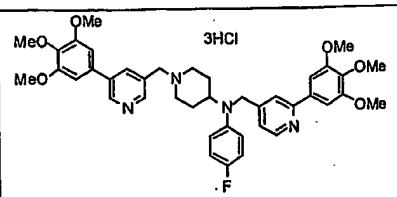
4-[N-(4-fluorophenyl)-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

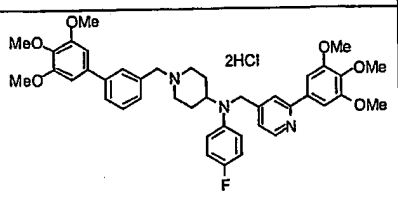
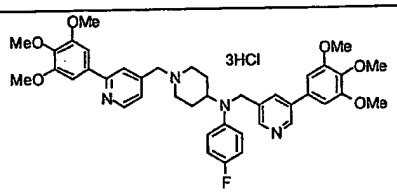
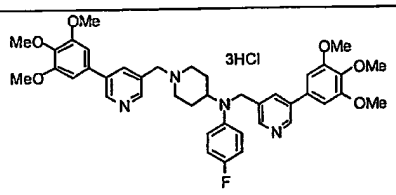
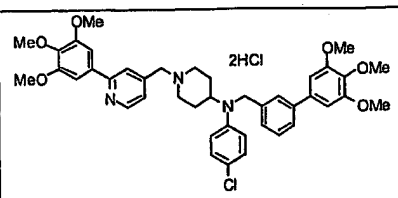


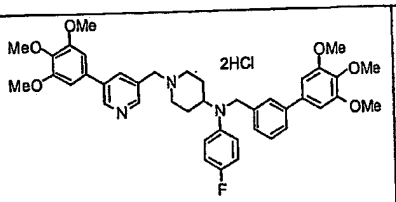
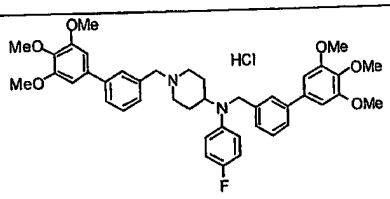
1-(tert-Butoxycarbonyl)-4-[N-(4-fluorophenyl)-N-[3-(3,4,5-trimethoxyphenyl) benzyl]amino]piperidine (1.01 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 790 mg (88%).

Example 157 to 164

These compounds were obtained by the condensation of amines obtained in Preparation Examples 181, 183 and 185 with chloride derivatives obtained in Preparation Examples 3, 42 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

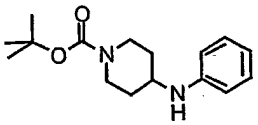
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
157		62%	1.60-1.82 (m, 2H), 1.83-1.91 (m, 2H), 2.13-2.23 (m, 2H), 2.95-3.03 (m, 2H), 3.57 (s, 2H), 3.64-3.75 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 3.96 (s, 6H), 4.48 (s, 2H), 6.65-6.70 (m, 2H), 6.90 (dd, 2H, J=8.8 Hz, 8.8 Hz), 7.13-7.16 (m, 3H), 7.20 (d, 1H, J=5.1 Hz), 7.22 (s, 2H), 7.54 (s, 1H), 7.59 (s, 1H), 8.55 (d, 1H, J=5.1 Hz), 8.59 (d, 1H, J=4.9 Hz).
158		53%	1.66-1.95 (m, 4H), 2.12-2.24 (m, 2H), 2.95-3.07 (m, 2H), 3.60 (s, 2H), 3.64-3.76 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.47 (s, 2H), 6.63-6.70 (m, 1H), 6.75 (s, 2H),

			6.90 (dd, 1H, J=9.2 Hz, 9.2 Hz), 7.11-7.16 (m, 3H), 7.53 (s, 1H), 7.77 (s, 1H), 8.50 (d, 1H, J=2.0 Hz), 8.55 (d, 1H, J=4.9 Hz), 8.70 (d, 1H, J=5.9 Hz).
159		51%	1.64-1.90 (m, 4H), 2.07-2.20 (m, 4H), 2.97-3.08 (m, 2H), 3.59 (s, 2H), 3.64-3.76 (m, 1H), 3.89 (s, 6H), 3.92 (s, 6H), 3.93 (s, 6H), 4.47 (s, 2H), 6.62-6.70 (m, 2H), 6.77 (s, 2H), 6.86-6.93 (m, 2H), 7.11-7.16 (m, 3H), 7.25-7.31 (m, 3H), 7.37 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.42-7.49 (m, 2H), 7.53 (s, 1H), 8.54 (d, 1H, J=5.1 Hz).
160		49%	1.74-1.98 (m, 4H), 2.10-2.30 (m, 2H), 2.90-3.12 (m, 2H), 3.53-3.73 (m, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.50 (s, 2H), 6.66 (s, 2H), 6.70-6.76 (m, 2H), 6.90 (dd, 2H, J=8.8 Hz, 8.8 Hz), 7.19-7.28 (m, 3H), 7.65 (br, 2H), 8.49 (d, 1H, J=1.8 Hz), 8.60 (d, 1H, J=4.9 Hz), 8.64 (d, 1H, J=2.2 Hz).
161		26%	1.67-1.97 (m, 4H), 2.10-2.27 (m, 2H), 2.94-3.06 (m, 2H), 3.56-3.68 (m, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.49 (s, 2H), 6.65 (s, 2H), 6.69-6.80 (m, 4H), 6.84-6.93 (m, 2H), 7.64 (s, 1H), 7.77 (br, 1H), 8.48 (d, 1H, J=1.7 Hz), 8.50 (d, 1H, J=1.7 Hz), 8.64 (d, 1H, J=1.9 Hz), 8.70 (s, 1H).
162		83%	1.72-1.92 (m, 4H), 2.12-2.21 (m, 2H), 2.94-3.02 (m, 2H), 3.57 (s, 2H), 3.64-3.74 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.51 (s, 1H), 6.66-6.71 (m, 4H), 6.88 (dd, 2H, J=8.6 Hz, 8.6 Hz), 7.18-7.27 (m, 4H), 7.34 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.39 (d, 2H, J=5.4 Hz), 7.59 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).

163		68%	1.68-1.87 (m, 4H), 2.10-2.22 (m, 2H), 2.94-3.04 (m, 2H), 3.59 (s, 2H), 3.65-3.74 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.49 (s, 2H), 6.66-6.70 (m, 6H), 6.88 (dd, 2H, J=8.8 Hz, 8.8 Hz), 7.19-7.40 (m, 4H), 7.77 (s, 1H), 8.49 (d, 1H, J=1.8 Hz), 8.70 (s, 1H).
164		74%	1.70-1.90 (m, 4H), 2.08-2.18 (m, 2H), 2.95-3.05 (m, 2H), 3.58 (s, 2H), 3.63-3.73 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.89 (s, 3H), 3.92 (s, 6H), 4.50 (s, 2H), 6.65-6.72 (m, 2H), 6.69 (s, 2H), 6.76 (s, 2H), 6.87 (dd, 2H, J=9.0 Hz, 9.0 Hz), 7.22 (d, 1H, J=7.6 Hz), 7.25-7.48 (m, 9H).

Preparation Example 186

Synthesis of 1-(tert-butoxycarbonyl)-4-phenylaminopiperidine:



1-(tert-Butoxycarbonyl)-4-piperidone (5.00 g) and aniline (2.23 g) was treated in the same manner as described in Preparation Example 37 to give white needles of the title compound.

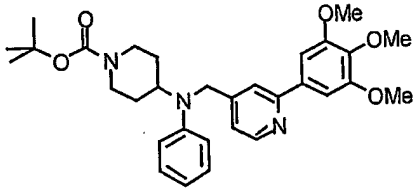
Yield: 3.77 g (57%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.25-1.38 (m, 2H), 1.47 (s, 9H), 2.00-2.07 (m, 2H), 2.87-2.97 (m, 2H), 3.38-3.53 (m, 2H), 3.96-4.14 (m, 2H), 6.57-6.52 (m, 2H), 6.70 (tt, 1H, J=6.2 Hz, 1.0 Hz), 7.17 (dd, 2H, J=8.6 Hz, 7.2 Hz).

Preparation Example 187

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-phenyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



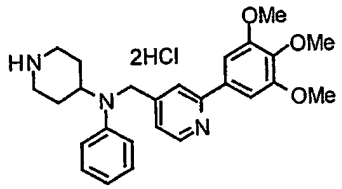
1-(tert-Butoxycarbonyl)-4-phenylaminopiperidine (553 mg) and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

Yield: 760 mg (71%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.53-1.63 (m, 2H), 1.83-1.91 (m, 2H), 2.76-2.90 (m, 2H), 3.86-3.97 (m, 1H), 3.89 (s, 3H), 3.93 (s, 6H), 4.14-4.32 (m, 2H), 4.49 (s, 2H), 6.71-6.78 (m, 3H), 7.14 (s, 1H), 7.15 (s, 2H), 7.21 (dd, 2H, J=8.8 Hz, 7.4 Hz), 7.55 (s, 1H), 8.56 (d, 1H, J=5.1 Hz).

Preparation Example 188

Synthesis of 4-[N-phenyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:

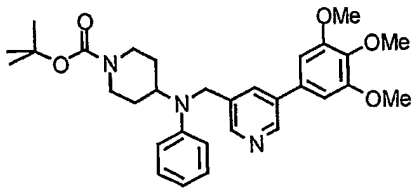


1-(tert-Butoxycarbonyl)-4-[N-phenyl-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (760 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 652 mg (90%).

Preparation Example 189

Synthesis of 1-(tert-butoxycarbonyl)-4-[N-phenyl-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine:



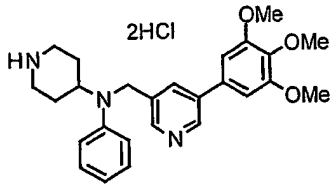
1-(tert-Butoxycarbonyl)-4-phenylaminopiperidine (553 mg) and 5-chloromethyl-3-(3,4,5-trimethoxyphenyl)pyridine (588 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.

Yield: 222 mg (21%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.52-1.67 (m, 2H), 1.82-1.91 (m, 2H), 2.74-2.87 (m, 2H), 3.88-3.90 (m, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 4.14-4.31 (m, 2H), 4.53 (s, 2H), 6.67 (s, 2H), 6.74-6.80 (m, 3H), 7.21 (dd, 2H, J=8.8 Hz, 7.2 Hz), 7.67 (s, 1H), 8.50 (d, 1H, J=5.3 Hz, 2.2 Hz), 8.66 (d, 1H, J=2.1 Hz).

Preparation Example 190

Synthesis of 4-[N-phenyl-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride:

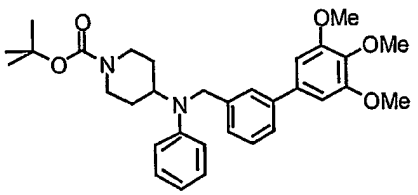


1-(tert-Butoxycarbonyl)-4-[N-phenyl-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine (222 mg) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.

Yield: 197 mg (94%).

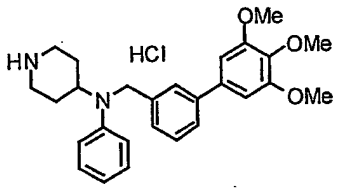
Preparation Example 191

Synthesis of 1-(tert-butoxycarbonyl)-4-[N-phenyl-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine:



1-(tert-Butoxycarbonyl)-4-phenylaminopiperidine (553 mg) and 3-(3,4,5-trimethoxyphenyl)benzyl chloride (586 mg) was treated in the same manner as described in Example 9 to give light yellow amorphous of the title compound.
Yield: 1.06 g (100%).
^{1}H-NMR (400 MHz, $CDCl_3$) δ : 1.45 (s, 9H), 1.52-1.68 (m, 2H), 1.83-1.92 (m, 2H), 2.73-2.86 (m, 2H), 3.88 (s, 3H), 3.89 (s, 6H), 3.94 (tt, 1H, J=11.7 Hz, 3.3 Hz), 4.14-4.30 (m, 2H), 4.52 (s, 2H), 6.69-6.78 (m, 6H), 7.17-7.27 (m, 2H), 7.32-7.42 (m, 3H).

Preparation Example 192
Synthesis of 4-[N-phenyl-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine hydrochloride:

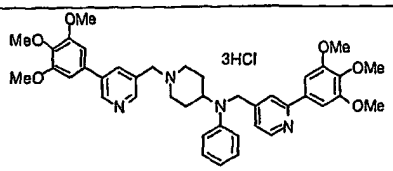
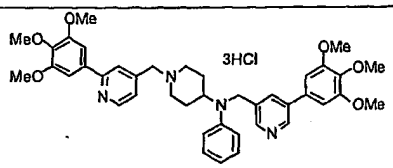
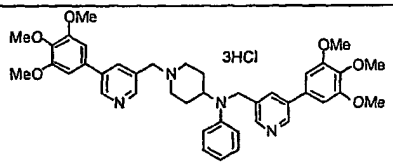
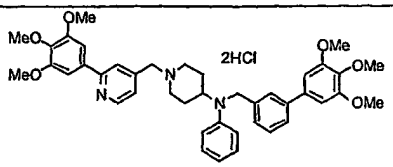
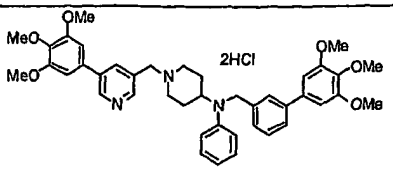


1-(tert-Butoxycarbonyl)-4-[N-phenyl-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]piperidine (1.06 g) was treated in the same manner as described in Preparation Example 94 to give light yellow powder of the title compound.
Yield: 909 mg (97%).

Example 165 to 169

These compounds were obtained by the condensation of amines obtained in Preparation Examples 188, 190 and 192 with chloride derivatives obtained in Preparation Examples 3 and 48. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

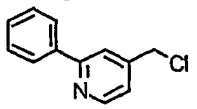
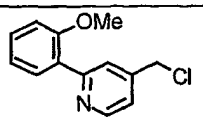
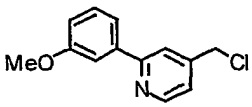
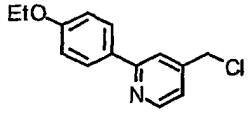
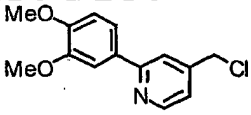
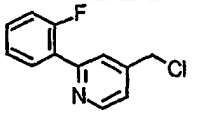
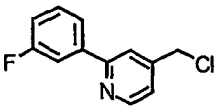
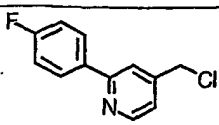
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ

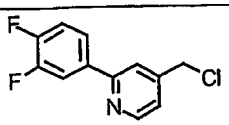
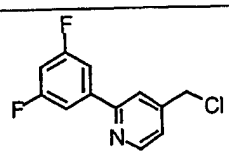
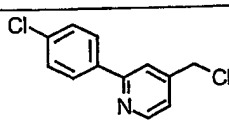
165		53%	1.63-1.81 (m, 4H), 1.82-1.92 (m, 2H), 2.14-2.24 (m, 2H), 2.95-3.05 (m, 2H), 3.59 (s, 2H), 3.80-4.02 (m, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 3.92 (s, 6H), 3.93 (s, 6H), 4.53 (s, 2H), 6.69-6.77 (m, 5H), 7.13-7.17 (m, 3H), 7.20 (dd, 2H, J=7.6 Hz, 7.6 Hz), 7.55 (s, 1H), 7.76 (s, 1H), 8.51 (d, 1H, J=1.8 Hz), 8.55 (d, 1H, J=5.1 Hz), 8.70 (s, 1H).
166		50%	1.85-2.04 (m, 4H), 2.20-2.40 (m, 2H), 2.92-3.25 (m, 2H), 3.60-3.77 (m, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 3.97 (s, 6H), 4.59 (s, 2H), 6.67 (s, 2H), 6.72-6.81 (m, 4H), 7.17-7.30 (m, 4H), 7.68 (s, 1H), 8.50 (s, 1H), 8.62 (d, 1H, J=4.9 Hz), 8.65 (d, 1H, J=2.0 Hz).
167		43%	1.72-1.92 (m, 4H), 2.13-2.26 (m, 2H), 2.95-3.04 (m, 2H), 3.59 (s, 2H), 3.78-4.01 (m, 1H), 3.88 (s, 9H), 3.90 (s, 3H), 3.93 (s, 6H), 4.56 (s, 2H), 6.66 (s, 2H), 6.70-6.78 (m, 5H), 7.19 (dd, 2H, J=8.2 Hz, 8.2 Hz), 7.66 (s, 1H), 7.77 (s, 1H), 8.50 (d, 1H, J=2.3 Hz), 8.51 (d, 1H, J=2.2 Hz), 8.65 (d, 1H, J=1.9 Hz), 8.70 (d, 1H, J=2.2 Hz).
168		82%	1.75-1.92 (m, 4H), 2.14-2.23 (m, 2H), 2.94-3.01 (m, 2H), 3.57 (s, 2H), 3.80-3.94 (m, 1H), 3.87 (s, 3H), 3.88 (s, 6H), 3.90 (s, 3H), 3.96 (s, 6H), 4.57 (s, 2H), 6.67-6.77 (m, 5H), 7.15-7.27 (m, 5H), 7.34 (dd, 1H, J=7.4 Hz, 7.4 Hz), 7.39 (d, 1H, 7.6 Hz), 7.42 (s, 1H), 7.59 (s, 1H), 8.59 (d, 1H, J=5.1 Hz).
169		65%	1.72-1.91 (m, 4H), 2.13-2.22 (m, 2H), 2.95-3.03 (m, 2H), 3.59 (s, 2H), 3.79-4.00 (m, 1H), 3.87 (s, 3H), 3.87 (s, 6H), 3.90 (s, 3H), 3.93 (s, 6H), 4.56 (s, 2H), 6.66-6.77 (m, 7H), 7.18 (dd, 2H, J=7.4 Hz, 7.4 Hz), 7.24 (d, 1H, J=7.4 Hz), 7.33 (dd, 1H, J=7.4 Hz,

			7.4 Hz), 7.38 (d, 1H, J=7.6 Hz), 7.41 (s, 1H), 7.76 (s, 1H), 8.50 (d, 1H, J=1.6 Hz), 8.69 (d, 1H, J=2.2 Hz).

Preparation Example 193 to 203

These compounds were prepared by the same procedure as described in Preparation Example from 1 to 3. Structures and NMR data are listed below.

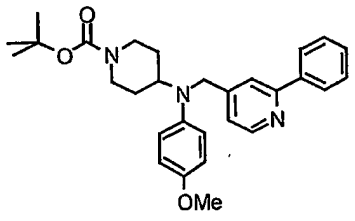
Preparation Example	Structure	NMR data (400 MHz, $CDCl_3$) δ
193		4.61 (s, 2H), 7.25 (d, 1H, J=1.2 Hz), 7.41-7.52 (m, 3H), 7.75 (d, 1H, J=0.8 Hz), 7.98-8.02 (m, 2H), 8.69 (d, 1H, J=4.9 Hz).
194		3.87 (s, 3H), 4.60 (s, 2H), 7.01 (d, 1H, J=8.4 Hz), 7.08 (t, 1H, J=7.4 Hz), 7.24 (dd, 1H, J=5.1 Hz, 1.4 Hz), 7.38 (dt, 1H, J=7.4 Hz, 1.8 Hz), 7.77 (dd, 1H, J=7.6 Hz, 1.8 Hz), 7.84 (s, 1H), 8.69 (d, 1H, J=5.1 Hz)
195		3.90 (s, 3H), 4.60 (s, 2H), 6.87-7.03 (1H, m), 7.39 (t, 1H, 7.8Hz), 7.50-7.66 (m, 2H), 7.73 (s, 1H), 8.68 (d, 1H, J=5.1 Hz)
196		1.45 (t, 3H, J=7.0 Hz), 4.12 (q, 2H, J=7.0 Hz), 4.59 (s, 2H), 6.99 (d, 2H, J=8.8 Hz), 7.18 (d, 1H, J=5.1 Hz), 7.20-7.29 (m, 1H), 7.68 (s, 1H), 7.95 (d, 2H, J=8.8 Hz), 8.63 (d, 1H, J=5.1 Hz)
197		3.95 (s, 3H), 4.00 (s, 3H), 4.60 (s, 2H), 6.96 (d, 1H, J=8.4 Hz), 7.21 (d, 1H, J=4.1 Hz), 7.53 (dd, 1H, J=8.4 Hz, 2.0 Hz), 7.67 (d, 1H, J=2.0 Hz), 7.70 (s, 1H), 8.65 (d, 1H, J=5.1 Hz)
198		4.61 (s, 2H), 7.14-7.21 (m, 1H), 7.21-7.23 (m, 2H), 7.35-7.42 (m, 1H), 7.80 (s, 1H), 7.98 (1H, dt, J=8.0 Hz, 2.0 Hz), 8.73 (d, 1H, J=5.1 Hz)
199		4.61 (s, 2H), 7.13 (1H, dt, J=8.4 Hz, 2.8 Hz), 7.28 (1H, d, J=5.0 Hz), 7.40-7.79 (m, 1H), 7.70-7.79 (m, 3H), 8.69 (d, 1H, J=5.0 Hz)
200		4.60 (s, 2H), 7.13-7.20 (m, 2H), 7.25 (1H, d, J=5.1 Hz), 7.70 (s, 1H), 7.95-8.03 (m, 2H), 8.66 (d, 1H, J=5.1 Hz)

201		4.61 (s, 2H), 7.21-7.30 (m, 2H), 7.69 (s, 1H), 7.73-7.76 (m, 1H), 7.85-7.92 (m, 1H), 8.76 (d, 1H, J=4.9 Hz)
202		4.61 (s, 2H), 6.86-6.91 (m, 1H), 7.31 (1H, d, J=5.1 Hz), 7.51-7.59 (m, 2H), 7.71 (s, 1H), 8.69 (d, 1H, J=5.1 Hz)
203		4.61 (s, 2H), 7.26 (d, 1H, J=4.9 Hz), 7.45 (d, 2H, J=8.4 Hz), 7.72 (s, 1H), 7.95 (d, 2H, J=8.4 Hz), 8.68 (s, 1H, J=4.9 Hz)

Preparation Example 204

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[(2-phenylpyridin-4-yl)methyl]amino]piperidine:



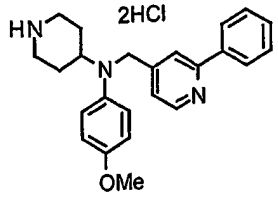
4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (612 mg) and 4-chloromethyl-2-phenylpyridine (204 mg) were condensed in the same manner as described in Example 9 to give the title compound.

Yield: 407 mg (43%).

Preparation Example 205

Synthesis of

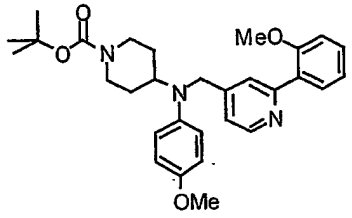
4-[N-(4-methoxyphenyl)-N-[(2-phenylpyridin-4-yl)methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[(2-phenylpyridin-4-yl)m

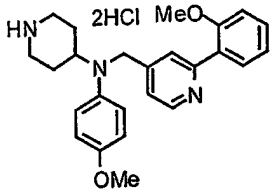
ethyl]amino]piperidine (407 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 365 mg (95%).

Preparation Example 206
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(2-methoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(2-methoxyphenyl)pyridine (234 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 237mg (72%).

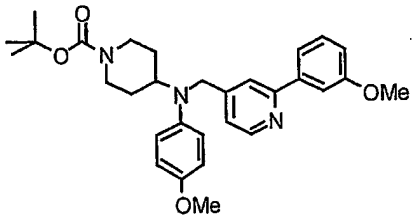
Preparation Example 207
Synthesis of
4-[N-(4-methoxyphenyl)-N-[[2-(2-methoxyphenyl)pyridin-4-yl]methyl]amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(2-methoxyphenyl)pyridin-4-yl]methyl]amino]piperidine (360 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 365mg (65%).

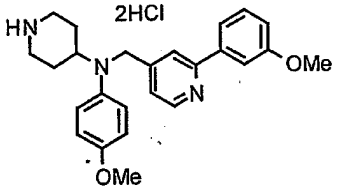
Preparation Example 208
Synthesis of

1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(3-methoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



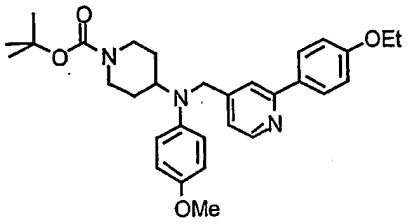
4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(3-methoxyphenyl)pyridine (234 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 550mg (theoretical yield).

Preparation Example 209
Synthesis of
4-[N-(4-methoxyphenyl)-N-[[2-(3-methoxyphenyl)pyridin-4-yl]methyl]amino]piperidin e dihydrochloride:



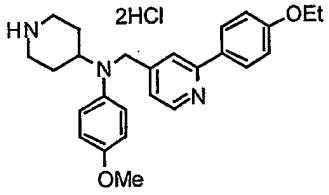
1-(tert-Butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(3-methoxyphenyl)py ridin-4-yl]methyl]amino]piperidine (550 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 436g (85%).

Preparation Example 210
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-[[2-(4-ethoxyphenyl)pyridin-4-yl]methyl]-N-(4-methoxyp henyl)]amino]piperidine:



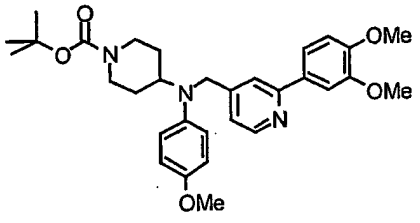
4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(4-ethoxyphenyl)pyridine (248 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 515 mg (99%).

Preparation Example 211
Synthesis of 4-[N-[[2-(4-ethoxyphenyl)pyridin-4-yl]methyl-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-[[2-(4-ethoxyphenyl)pyridin-4-yl]methyl-N-(4-methoxyphenyl)amino]piperidine (515 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 418 mg (80%).

Preparation Example 212
Synthesis of 1-(tert-butoxycarbonyl)-4-[N-(4-methoxyphenyl)-N-[[2-(3,4-dimethoxyphenyl)pyridin-4-yl]methyl]amino]piperidine:



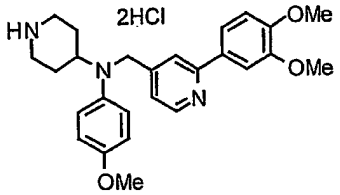
4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(3,4-dimethoxyphenyl)pyridine (264 mg) were condensed in the same manner as described in Example 9 to give the title compound.

Yield: 600 mg (theoretical yield).

Preparation Example 213

Synthesis of

4-[N-[[2-(3,4-dimethoxyphenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:



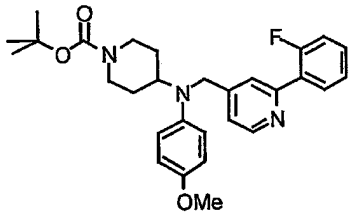
1-(tert-Butoxycarbonyl)-4-[N-[[2-(3,4-dimethoxyphenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine (600 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.

Yield: 416 mg (77%).

Preparation Example 214

Synthesis of

1-(tert-butoxycarbonyl)-4-[N-[[2-(2-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine:



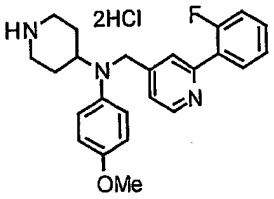
4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(2-fluorophenyl)pyridine (222 mg) were condensed in the same manner as described in Example 9 to give the title compound.

Yield: 530 mg (theoretical yield).

Preparation Example 215

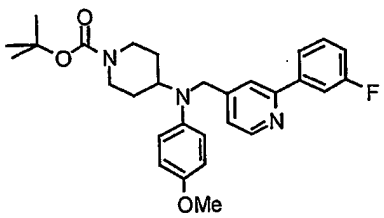
Synthesis of

4-[N-[[2-(2-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:



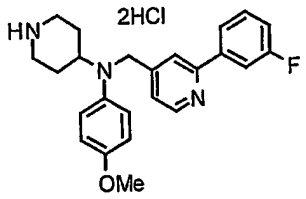
1-(tert-Butoxycarbonyl)-4-[N-[[2-(2-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine (530 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 423mg (85%).

Preparation Example 216
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-[[2-(3-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine:



4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (153 mg) and 4-chloromethyl-2-(3-fluorophenyl)pyridine (111 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 270 mg (theoretical yield).

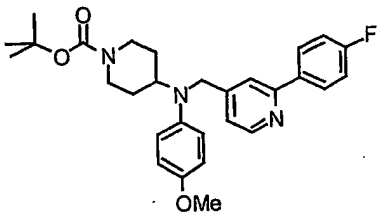
Preparation Example 217
Synthesis of
4-[[[2-(3-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-[[2-(3-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine (270 mg) was treated in the same manner as described

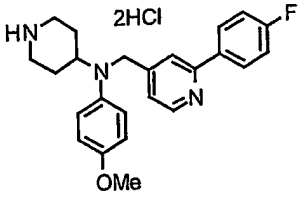
in Preparation Example 94 to give the title compound.
Yield: 193 mg (70%).

Preparation Example 218
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-[[2-(4-fluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine:



4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(4-fluorophenyl)pyridine (222 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 550 mg (theoretical yield).

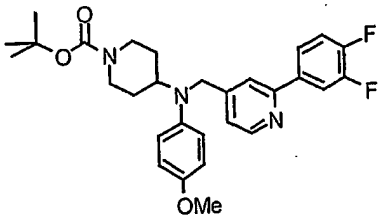
Preparation Example 219
Synthesis of
4-[N-[[2-(4-fluorophenyl)pyridin-4-yl]methyl-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-[[2-(4-fluorophenyl)pyridin-4-yl]methy]-l-N-(4-methoxyphenyl)amino]piperidine (550 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 439 mg (88%).

Preparation Example 220
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-[[2-(3,4-difluorophenyl)pyridin-4-yl]methyl]-N-(4-metho

xyphenyl)amino]piperidine:

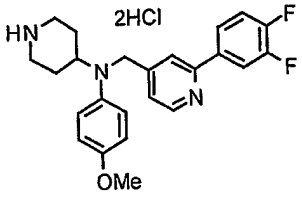


4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(3,4-difluorophenyl)pyridine (240 mg) were condensed in the same manner as described in Example 9 to give the title compound.

Yield: 590 mg (theoretical yield).

Preparation Example 221

Synthesis of 4-[N-[[2-(3,4-difluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:

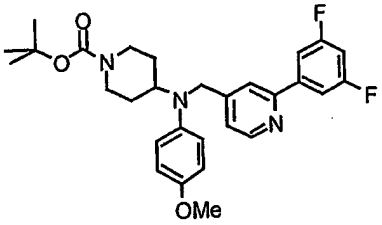


1-(tert-Butoxycarbonyl)-4-[-N-[[2-(3,4-difluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine (590 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.

Yield: 483 mg (93%).

Preparation Example 222

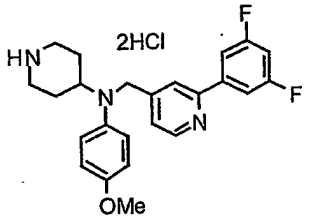
Synthesis of 1-(tert-butoxycarbonyl)-4-[N-[[2-(3,5-difluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine:



4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and

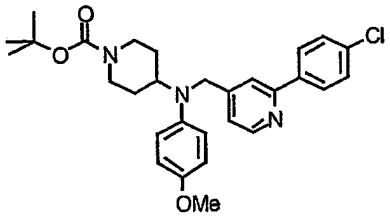
4-chloromethyl-2-(3,5-difluorophenyl)pyridine (240 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 530 mg (theoretical yield).

Preparation Example 223
Synthesis of
4-[N-[[2-(3,5-difluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:



1-(tert-Butoxycarbonyl)-4-[N-[[2-(3,5-difluorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine: (530 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 418 mg (81%).

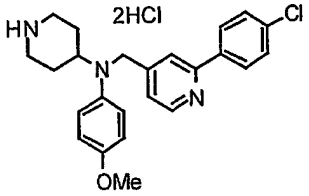
Preparation Example 224
Synthesis of
1-(tert-butoxycarbonyl)-4-[N-[[2-(4-chlorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine:



4-(*p*-Anisidino)-1-(tert-butoxycarbonyl)piperidine (306 mg) and 4-chloromethyl-2-(4-chlorophenyl)pyridine (238 mg) were condensed in the same manner as described in Example 9 to give the title compound.
Yield: 600 mg (theoretical yield).

Preparation Example 225

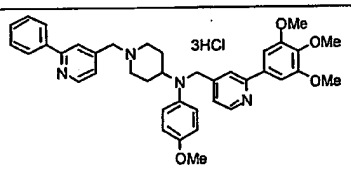
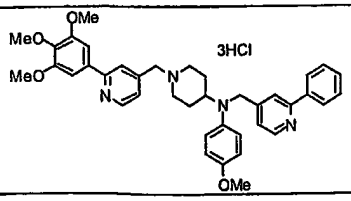
Synthesis of
4-[N-[[2-(4-chlorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine dihydrochloride:

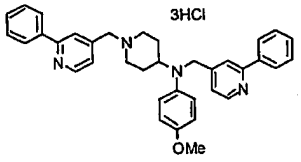
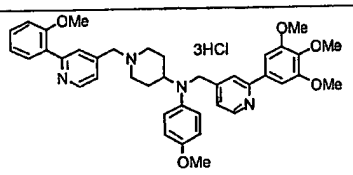
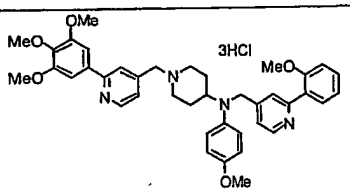
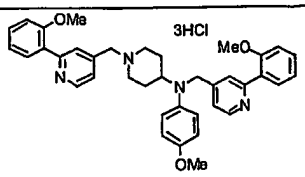


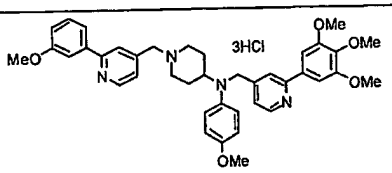
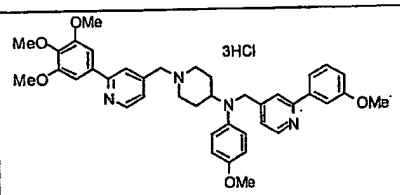
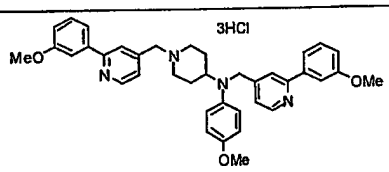
1-(tert-Butoxycarbonyl)-4-[N-[[2-(4-chlorophenyl)pyridin-4-yl]methyl]-N-(4-methoxyphenyl)amino]piperidine: (600 mg) was treated in the same manner as described in Preparation Example 94 to give the title compound.
Yield: 447 mg (86%).

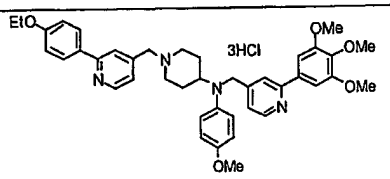
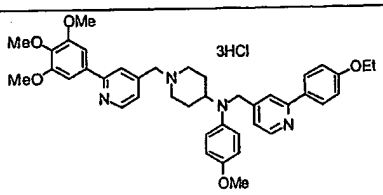
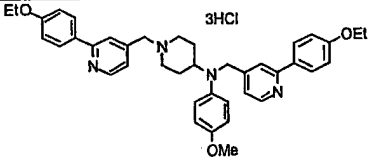
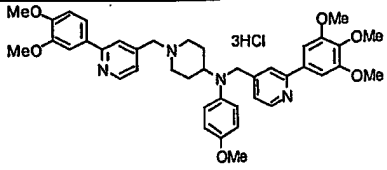
Examples 170 to 202

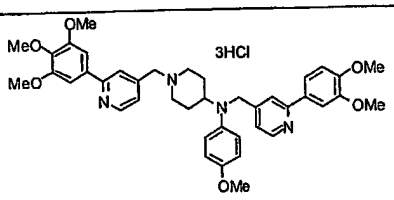
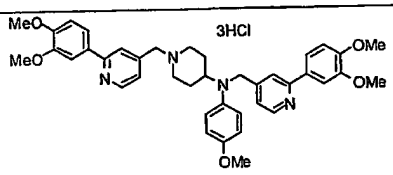
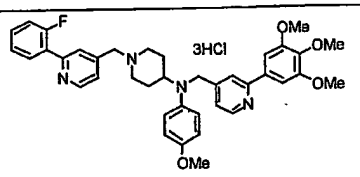
These compounds were obtained by the condensation of amines obtained in Preparation Examples 96, 205, 207, 209, 211, 213, 215, 217, 219, 221, 223 and 225 with chloride derivatives obtained in Preparation Examples 3, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102 and 103. Free bases obtained were then converted to the corresponding hydrochlorides. Yields and NMR data of their free bases are listed below.

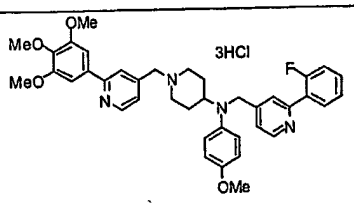
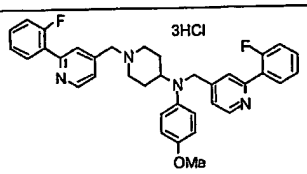
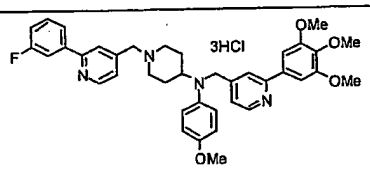
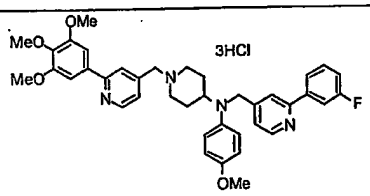
Example	Structure	Yield	NMR data (400 MHz, measured as free bases, $CDCl_3$) δ
170		47%	1.67-1.80 (m, 2H), 1.83-1.91 (m, 2H), 2.10-2.19 (m, 2H), 2.93-3.00 (m, 2H), 3.54-3.65 (m, 1H), 3.56 (s, 2H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.45 (s, 3H), 6.73 (d, 2H, J=9.4 Hz), 6.78 (d, 2H, J=9.4 Hz), 7.14-7.21 (m, 2H), 7.15 (s, 2H), 7.38-7.49 (m, 3H), 7.57 (s, 1H), 7.68 (s, 1H), 7.97 (d, 1H, J=1.0 Hz), 7.99 (d, 1H, J=1.6 Hz), 8.54 (d, 1H, J=5.1 Hz), 8.61 (d, 1H, J=5.1 Hz).
171		55%	1.62-1.80 (m, 2H), 1.84-1.93 (m, 2H), 2.10-2.20 (m, 2H), 2.93-3.02 (m, 2H), 3.53-3.66 (m, 1H), 3.56 (s, 2H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.44 (s, 2H),

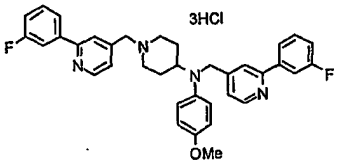
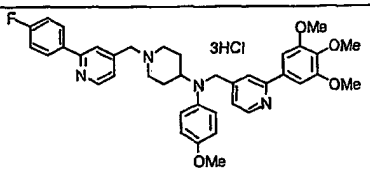
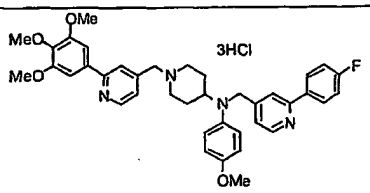
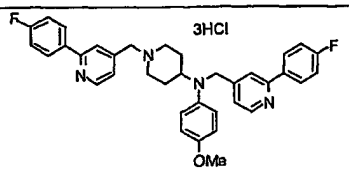
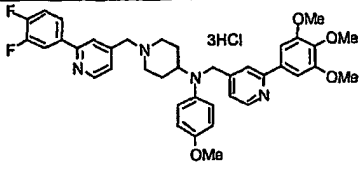
			6.65-6.83 (m, 4H), 7.14-7.30 (m, 4H), 7.36-7.50 (m, 3H), 7.59 (s, 1H), 7.67 (s, 1H), 7.93 (d, 2H, J=7.0 Hz), 8.54-8.61 (m, 2H).
172		54%	1.67-1.92 (m, 4H), 2.08-2.20 (m, 2H), 2.92-3.01 (m, 2H), 3.52-3.65 (m, 1H), 3.55 (s, 2H), 3.72 (s, 3H), 4.38 (s, 2H), 6.72 (d, 2H, J=9.2 Hz), 6.78 (d, 2H, J=9.0 Hz), 7.18 (dd, 2H, J=4.9 Hz, 4.9 Hz), 7.36-7.50 (m, 6H), 7.67 (s, 1H), 7.68 (s, 1H), 7.93 (dd, 2H, J=8.4 Hz, 1.2 Hz), 7.98 (dd, 2H, J=8.6 Hz, 1.4 Hz), 8.57 (d, 1H, J=5.1 Hz), 8.60 (d, 1H, J=5.1 Hz).
173		100%	1.66-1.79 (m, 2H), 1.82-1.91 (m, 2H), 2.09-2.20 (m, 2H), 2.93-3.03 (m, 2H), 3.56 (s, 2H), 3.56-3.59 (m, 1H), 3.73 (s, 3H), 3.80 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.45 (s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.98 (d, 1H, J=8.5 Hz), 7.07 (t, 1H J=7.6 Hz), 7.15 (s, 2H), 7.15-7.19 (m, 2H), 7.33-7.38 (m, 1H), 7.57 (s, 1H), 7.66-7.74 (m, 2H), 8.53 (d, 1H, J=5.1 Hz), 8.61 (d, 1H, J=4.9 Hz).
174		94%	1.70-1.80 (m, 2H), 1.83-1.91 (m, 2H), 2.11-2.18 (m, 2H), 2.92-3.01 (m, 2H), 3.56 (s, 2H), 3.57-3.65 (m, 1H), 3.73 (s, 3H), 3.74 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.44 (s, 2H), 6.71 (d, 2H, J=9.0 Hz), 6.78 (d, 2H, J=9.0 Hz), 6.96 (d, 1H, J=8.3 Hz), 7.05 (dt, 1H. J=7.3 Hz, 1.0 Hz), 7.14 (d, 1H, J=5.2 Hz), 7.20 (d, 1H, J=5.2 Hz), 7.22 (2H, s), 7.32-7.37 (m, 1H), 7.59 (s, 1H), 7.71-7.75 (m, 2H), 8.56-8.60 (m, 2H).
175		98%	1.67-1.80 (m, 2H), 1.83-1.90 (m, 2H), 2.10-2.19 (m, 2H), 2.94-3.03 (m, 2H), 3.50-3.67 (m, 1H), 3.56 (s, 2H), 3.73 (s, 3H), 3.74 (s, 3H), 3.79 (s, 3H), 4.44 (s, 2H), 6.70 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.96 (d, 1H, J=8.3 Hz), 6.98

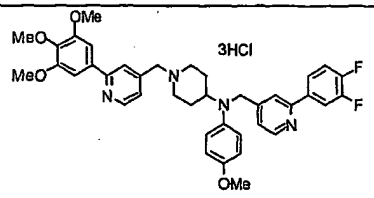
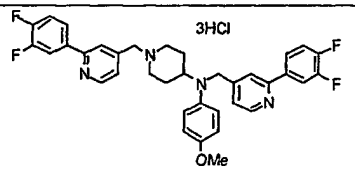
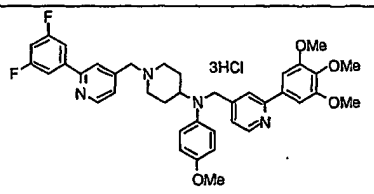
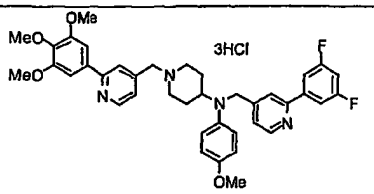
			(d, 1H, J=8.8 Hz), 7.04 (dd, 1H, J=7.6 Hz, 1.0 Hz), 7.07 (dd, 1H, 7.6, J=1.0 Hz), 7.12-7.19 (m, 2H), 7.32-7.39 (m, 2H), 7.70-7.75 (m, 4H), 8.58 (d, 1H, J=5.1 Hz), 8.61 (d, 1H, J=4.9 Hz).
176		100%	1.68-1.79 (m, 2H), 1.82-1.90 (m, 2H), 2.10-2.19 (m, 2H), 2.90-3.01 (m, 2H), 3.56 (s, 2H), 3.56-3.58 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.91 (s, 3H), 3.93 (s, 6H), 4.45(s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.93-6.99 (m, 1H), 7.15 (s, 2H), 7.16-7.20 (m, 2H), 7.37 (t, 1H, J=7.8 Hz), 7.52-7.59 (m, 3H), 7.67 (s, 1H), 8.54 (d, 1H, J=5.1 Hz), 8.60 (d, 1H, J=5.1 Hz).
177		100%	1.68-1.79 (m, 2H), 1.83-1.92 (m, 2H), 2.11-2.16 (m, 2H), 2.91-3.02 (m, 2H), 3.56 (s, 2H), 3.55-3.65 (m, 1H), 3.73 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.43 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.95 (dd, 1H. J=8.3 Hz, 2.7 Hz), 7.16-7.21 (m, 2H), 7.22 (s, 2H), 7.35 (t, 1H, J=7.8 Hz), 7.48 (d, 1H, J=7.8 Hz), 7.53 (t, 1H, J=2.7 Hz), 7.59 (s, 1H), 7.65 (s, 1H), 8.55-8.60 (m, 2H).
178		100%	1.65-1.79 (m, 2H), 1.82-1.90 (m, 2H), 2.09-2.19 (m, 2H), 2.92-3.00 (m, 2H), 3.50-3.66 (m, 1H), 3.56 (s, 2H), 3.73 (s, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.44 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.92-6.98 (m, 2H), 7.16-7.21 (m, 2H), 7.34 (d, 1H, J=7.8 Hz), 7.38 (d, 1H, J=8.5 Hz), 7.46-7.59 (m, 4H), 7.65 (s, 1H), 7.67 (s, 1H), 8.57 (dd, 1H, J=5.1 Hz, 0.7 Hz), 8.60 (d, 1H, J=5.1 Hz).

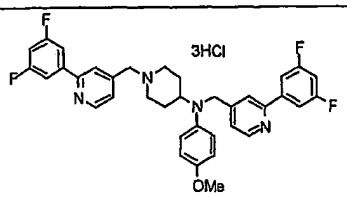
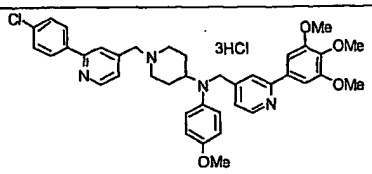
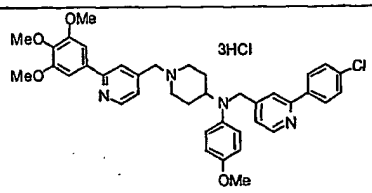
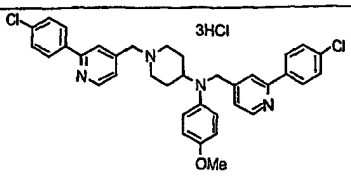
179		76%	1.44 (t, 3H, J=7.1 Hz), 1.70-1.80 (m, 2H), 1.82-1.91 (m, 2H), 2.10-2.19 (m, 2H), 2.90-3.02 (m, 2H), 3.54 (s, 2H), 3.73-3.78 (m, 1H), 3.73 (s, 3H), 3.88 (s, 3H), 3.93 (s, 6H), 4.09 (q, 2H, J=7.1 Hz), 4.45 (s, 2H), 6.73 (d, 2H, J=9.2 Hz), 6.78 (d, 2H, J=9.2 Hz), 6.97 (d, 2H, J=8.8 Hz), 7.10-7.18 (m, 2H), 7.15 (s, 2H), 7.57 (s, 1H), 7.61 (s, 1H), 7.92 (d, 2H, J=8.8 Hz), 8.52-8.58 (m, 2H).
180		93%	1.43 (t, 3H, J=6.8 Hz), 1.68-1.80 (m, 2H), 1.82-1.92 (m, 2H), 2.10-2.19 (m, 2H), 2.90-3.01 (m, 2H), 3.56 (s, 2H), 3.57-3.64 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.08 (q, 2H, J=6.8 Hz), 4.42 (s, 2H), 6.72 (d, 2H, J=9.0 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.95 (d, 2H, J=8.8 Hz), 7.11 (d, 1H, J=5.1 Hz), 7.20 (d, 1H, J=5.1 Hz), 7.22 (s, 2H), 7.58-7.62 (m, 2H), 7.87 (d, 2H, J=8.8 Hz), 8.52 (d, 1H, J=5.1 Hz), 8.58 (d, 1H, J=5.1 Hz).
181		100%	1.43 (t, 3H, J=7.1 Hz), 1.44 (t, 3H, J=7.1 Hz), 1.67-1.78 (m, 2H), 1.82-1.90 (m, 2H), 2.09-2.18 (m, 2H), 2.92-3.00 (m, 2H), 3.54 (s, 2H), 3.55-3.65 (m, 1H), 3.73 (s, 3H), 4.08 (q, 2H, J=7.1 Hz), 4.09 (q, 2H, J=6.8 Hz), 4.42 (s, 2H), 6.71 (d, 2H, J=9.0 Hz), 6.78 (d, 2H, J=9.0 Hz), 6.93-7.00 (m, 4H), 7.10-7.14 (m, 2H), 7.60 (s, 2H), 7.88 (s, 2H), 7.88 (d, 2H, J=8.8 Hz), 7.93 (d, 2H, J=8.8 Hz), 8.52 (d, 1H, J=5.1 Hz), 8.56 (d, 1H, J=4.9 Hz).
182		100%	1.68-1.79 (m, 2H), 1.82-1.90 (m, 2H), 2.10-2.19 (m, 2H), 2.90-3.01 (m, 2H), 3.55 (s, 2H), 3.56-3.59 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 3.94 (s, 3H), 3.99 (s, 3H), 4.45 (s, 2H), 6.76 (d, 2H, J=9.5 Hz), 6.78 (d, 2H, J=9.5 Hz),

			6.94 (d, 1H, J=8.3 Hz), 7.15 (s, 2H), 7.16-7.19 (m, 2H), 7.49-7.66 (m, 4H), 8.54 (d, 1H, J=4.9 Hz), 8.57 (d, 1H, J=5.1 Hz).
183		100%	1.68-1.78 (m, 2H), 1.82-1.91 (m, 2H), 2.10-2.18 (m, 2H), 2.93-3.00 (m, 2H), 3.56 (s, 2H), 3.56-3.62 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 3.96 (s, 6H), 3.97 (S, 3H), 4.43 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.92 (d, 1H, J=8.3 Hz), 7.12 (d, 1H, J=5.1 Hz), 7.20 (d, 1H, J=5.1 Hz), 7.22 (s, 2H), 7.42 (d, 1H, J=8.5 Hz, 2.2Hz), 7.58-7.63 (m, 3H), 8.53 (d, 1H, J=4.9 Hz), 8.58 (d, 1H, J=5.1 Hz).
184		89%	1.67-1.79 (m, 2H), 1.84-1.90 (m, 2H), 2.10-2.19 (m, 2H), 2.93-3.01 (m, 2H), 3.50-3.65 (m, 1H), 3.55 (s, 2H), 3.73 (s, 3H), 3.94 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 4.43 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.92 (d, 1H, J=8.6 Hz), 6.94 (d, 1H, J=8.3 Hz), 7.14 (d, 1H, J=5.6 Hz), 7.15 (d, 1H, J=6.4 Hz), 7.43 (dd, 1H, J=8.6 Hz, 2.0 Hz), 7.50 (dd, 1H, J=8.3 Hz, 1.9 Hz), 7.60-7.63 (m, 3H), 7.66 (d, 1H, J=2.2 Hz), 8.53 (d, 1H, J=5.1 Hz), 8.57 (d, 1H, J=4.9 Hz).
185		100%	1.68-1.79 (m, 2H), 1.82-1.90 (m, 2H), 2.10-2.20 (m, 2H), 2.93-3.01 (m, 2H), 3.57 (s, 2H), 3.57-3.65 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.46 (s, 2H), 6.73 (d, 2H, J=7.3 Hz), 6.78 (d, 2H, J=7.3 Hz), 7.11-7.19 (m, 2H), 7.15 (s, 2H), 7.22-7.29 (m, 2H), 7.34-7.40 (m, 1H), 7.58 (s, 1H), 7.73 (s, 1H), 7.94 (t, 1H, J=8.3 Hz), 8.54 (d, 1H, J=5.1 Hz), 8.64 (d, 1H, J=4.9 Hz).

186		88%	1.68-1.79 (m, 2H), 1.83-1.92 (m, 2H), 2.09-2.16 (m, 2H), 2.93-3.01 (m, 2H), 3.56 (s, 2H), 3.56-3.62 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.44(s, 2H), 6.71 (d, 2H, J=9.3 Hz), 6.77 (d, 2H, J=9.3 Hz), 7.10-7.16 (m, 1H), 7.17-7.26 (m,3H), 7.22 (s, 2H), 7.32-7.38 (m, 1H), 7.59 (s, 1H), 7.73 (s, 1H) , 7.92 (dt, 1H, J=8.0 Hz, 2.0 Hz), 8.57-8.61(m, 2H).
187		100%	1.66-1.80 (m, 2H), 1.83-1.93 (m, 2H), 2.10-2.20 (m, 2H), 2.92-3.02 (m, 2H), 3.53-3.65 (m, 1H), 3.57 (s, 2H), 3.73 (s, 3H), 4.44 (s, 2H), 6.71 (d, 2H, J=9.0 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.10-7.18 (m, 2H), 7.19-7.29 (m, 4H), 7.32-7.40 (m, 2H), 7.73 (s, 2H), 7.91 (dd, 1H, J=8.1 Hz, 1.4 Hz), 7.95 (dd, 1H, J=7.6 Hz, 1.5 Hz), 8.60 (d, 1H, J=4.9 Hz), 8.64 (d, 1H, J=5.1 Hz).
188		96%	1.67-1.80 (m, 2H), 1.82-1.92 (m, 2H), 2.10-2.20 (m, 2H), 2.91-3.01 (m, 2H), 3.56 (s, 2H), 3.56-3.61(m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.46 (s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.06-7.19 (m, 2H), 7.15 (s, 2H), 7.20-7.26 (m, 1H), 7.38-7.45 (m, 1H), 7.56 (s,1H), 766-7.78 (m, 3H), 8.54 (d, 1H, J=5.1 Hz), 8.61 (d, 1H, J=4.9 Hz).
189		92%	1.65-1.78 (m, 2H), 1.79-1.92 (m, 2H), 2.21-2.26 (m, 2H), 2.90-3.01 (m, 2H), 3.56 (s, 2H), 3.56-3.63 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.44 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.08 (dt, 1H, J=8.3 Hz, 1.7 Hz), 7.18-7.40 (m, 2H), 7.22 (s, 2H), 7.37-7.43 (m, 1H), 7.56-7.72 (m, 4H), 8.55-8.60 (m, 2H).

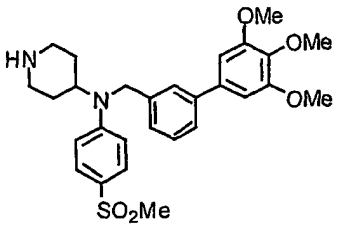
190		55%	1.66-1.79 (m, 2H), 1.80-1.91 (m, 2H), 2.10-2.20 (m, 2H), 2.88-3.01 (m, 2H), 3.50-3.66 (m, 1H), 3.56 (s, 2H), 3.73 (s, 3H), 4.45 (s, 2H), 6.72 (d, 2H, J=8.5 Hz), 6.79 (d, 2H, J=9.0 Hz), 7.04-7.13 (m, 2H), 7.19-7.25 (m, 2H), 7.35-7.46 (m, 2H), 7.62-7.79 (m, 6H), 8.57 (d, 1H, J=5.1 Hz), 8.61 (d, 1H, J=4.9 Hz).
191		100%	1.68-1.79 (m, 2H), 1.82-1.91(m, 2H), 2.10-2.19 (m, 2H), 2.92-3.00 (m, 2H), 3.55 (s, 2H), 3.56-3.63 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.45(s, 2H), 6.73(d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.11-7.19 (m, 4H), 7.15 (s, 2H), 7.57 (s, 1H), 7.63 (s, 1H), 7.92-8.01 (m, 2H), 8.54 (d, 1H, J=5.1 Hz), 8.58 (d, 1H, J=5.1 Hz).
192		100%	1.68-1.79 (m, 2H), 1.83-1.92 (m, 2H), 2.11-2.19 (m, 2H), 2.93-3.01 (m, 2H), 3.56 (s, 2H), 3.57-3.62 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.43 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.10-7.22 (m, 4H), 7.22 (s, 2H), 7.54-7.66 (m, 2H), 7.88-7.94 (m, 2H), 8.55 (d, 1H, J=4.9 Hz), 8.58 (d, 1H, J=4.9 Hz).
193		90%	1.66-1.80 (m, 2H), 1.83-1.91 (m, 2H), 2.10-2.19 (m, 2H), 2.92-3.00 (m, 2H), 3.50-3.66 (m, 1H), 3.55 (s, 2H), 3.73 (s, 3H), 4.44 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 7.78 (d, 2H, J=9.3 Hz), 7.09-7.20 (m, 6H), 7.62 (s, 1H), 7.63 (s, 1H), 7.89-8.00 (m, 4H), 8.55 (d, 1H, J=5.1 Hz), 8.58 (d, 1H, J=4.9 Hz).
194		36%	1.68-1.80 (m, 2H), 1.82-1.90 (m, 2H), 2.11-2.19 (m, 2H), 2.91-2.99 (m, 2H), 3.55 (s, 2H), 3.56-3.62 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.45 (s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.15 (s, 2H), 7.16-7.26 (m, 3H), 7.57 (s, 1H), 7.62 (s, 1H),

			7.71 (br, 1H), 7.80-7.90 (m, 1H), 8.54 (d, 1H, J=5.1 Hz), 8.58 (d, 1H, J=4.9 Hz).
195		100%	1.60-1.80 (m, 2H), 1.82-1.91 (m, 2H), 2.12-2.19 (m, 2H), 2.91-3.00 (m, 2H), 3.56 (s, 2H), 3.56-3.64 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.45 (s, 2H), 6.72 (d, 2H, J=9.0 Hz), 6.78 (d, 2H, J=9.0 Hz), 7.17-7.24 (m, 4H), 7.25-7.27 (m, 1H), 7.60 (s, 2H), 7.65 (br, 1H), 7.77-7.84 (m, 1H), 8.53-8.61 (m, 2H).
196		100%	1.66-1.79 (m, 2H), 1.82-1.91 (m, 2H), 2.09-2.20 (m, 2H), 2.90-3.00 (m, 2H), 3.50-3.65 (m, 1H), 3.55 (s, 2H), 3.73 (s, 3H), 4.44 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.79 (d, 2H, J=9.3 Hz), 7.18-7.28 (m, 4H), 7.60 (s, 1H), 7.62 (s, 1H), 7.63-7.68 (m, 1H), 7.70-7.75 (m, 1H), 7.77-7.89 (m, 2H), 8.55 (d, 1H, J=4.9 Hz), 8.58 (d, 1H, J= 5.1 Hz).
197		100%	1.68-1.80 (m, 2H), 1.82-1.90 (m, 2H), 2.10-2.21 (m, 2H), 2.90-3.00 (m, 2H), 3.56 (s, 2H), 3.56-3.63 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.56 (s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 6.81-6.87 (m, 1H), 7.15 (s, 2H), 7.18 (d, 1H, J=4.2 Hz), 7.22-7.26 (m, 1H), 7.51-7.59 (m, 3H), 7.65 (s, 1H), 8.54 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J= 5.1 Hz).
198		100%	1.65-1.79 (m, 2H), 1.80-1.94 (m, 2H), 2.22-2.25 (m, 2H), 2.90-3.05 (m, 2H), 3.56 (s, 2H), 3.56-3.65 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.44 (s, 2H), 6.72 (d, 2H, J=9.2 Hz), 6.78 (d, 2H, J=9.2 Hz), 6.80-6.94 (m, 2H), 7.22 (s, 2H), 7.19-7.28 (m, 1H), 7.45-7.51 (m, 2H), 7.59 (s, 1H), 7.62 (s, 1H), 8.56 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J= 5.1 Hz).

199		100%	1.67-1.79 (m, 2H), 1.82-1.92 (m, 2H), 2.12-2.20 (m, 2H), 2.92-2.99 (m, 2H), 3.50-3.65 (m, 1H), 3.56 (s, 2H), 3.73 (s, 3H), 4.45 (s, 2H), 6.72 (d, 2H, J=9.0 Hz), 6.79 (d, 2H, J=9.3 Hz), 6.80-6.88 (m, 2H), 7.23-7.27 (m, 2H), 7.48 (dd, 2H, J=8.8 Hz, 2.2 Hz), 7.55 (dd, 2H, J=8.8 Hz, 2.2 Hz), 7.63 (s, 1H), 7.65 (s, 1H), 8.57 (d, 1H, J=4.9 Hz), 8.60 (d, 1H, J=4.9 Hz).
200		84%	1.68-1.80 (m, 2H), 1.83-1.92 (m, 2H), 2.10-2.21(m, 2H), 2.91-3.00 (m, 2H), 3.56 (s, 2H), 3.57-3.62 (m, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 3.93 (s, 6H), 4.45 (s, 2H), 6.73 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.15 (s, 2H), 7.17 (d, 1H, J=4.9 Hz), 7.20 (d, 1H, J=5.1 Hz), 7.43 (d, 2H, J=8.3 Hz), 7.57 (s, 1H), 7.65 (s, 1H), 7.93 (d, 2H, J=8.3 Hz), 8.54 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=5.1 Hz).
201		72%	1.65-1.78 (m, 2H), 1.82-1.91 (m, 2H), 2.10-2.16 (m, 2H), 2.91-3.02 (m, 2H), 3.56 (s, 2H), 3.56-3.64 (m, 1H), 3.73 (s, 3H), 3.90 (s, 3H), 3.96 (s, 6H), 4.43 (s, 2H), 6.72 (d, 2H, J=9.3 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.17-7.21 (m, 1H), 7.22 (2H, s), 7.41 (d, 2H, J=8.7 Hz), 7.48 (d, 1H, J=7.8 Hz), 7.59 (s, 1H), 7.63 (s, 1H) 7.87 (d, 2H, J=8.7 Hz), 8.56 (d, 1H, J=4.9 Hz), 8.58 (d, 1H, J=5.1 Hz).
202		94%	1.67-1.88 (m, 2H), 1.83-1.90 (m, 2H), 2.10-2.17 (m, 2H), 2.92-2.99 (m, 2H), 3.50-3.65 (m, 1H), 3.55 (s, 2H), 3.73 (s, 3H), 4.44 (s, 2H), 6.72 (d, 2H, J=9.0 Hz), 6.78 (d, 2H, J=9.3 Hz), 7.17-7.22 (m, 2H), 7.39-7.45 (m, 4H), 7.63 (s, 1H), 7.65 (s, 1H), 7.88 (d, 2H, J=8.6 Hz), 7.93 (d, 2H, J=8.5 Hz), 8.56 (d, 1H, J=4.9 Hz), 8.59 (d, 1H, J=4.9 Hz).

Preparation Example 226

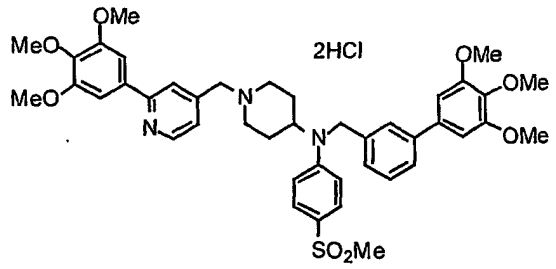
Synthesis of 4-[N-[3-(3,4,5-trimethoxyphenyl)benzyl] -N-[4-(methylsulfonyl)phenyl] amino]piperidine:



To a solution of 4-[N-[3-(3,4,5-trimethoxyphenyl)benzyl]-N-[4-(methylthio)phenyl]amino]piperidine hydrochloride (52 mg, obtained in the Preparation Example 145) in dichloromethane (1 mL) was added 3-chloroperbenzoic acid (69 mg) at 0°C. The mixture was stirred at room temperature for 3 hours and saturated aqueous sodium hydrogen carbonate was added. After separating the organic layer, the aqueous layer was extracted with chloroform. Organic layers were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated to give pale yellow oil of the title compound which was used for the next step without further purification.

Example 203

Synthesis of 4-[[N-[4-(methylsulfonyl)phenyl]-N-[3-(3,4,5-trimethoxyphenyl)benzyl]amino]-1-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]piperidine dihydrochloride:



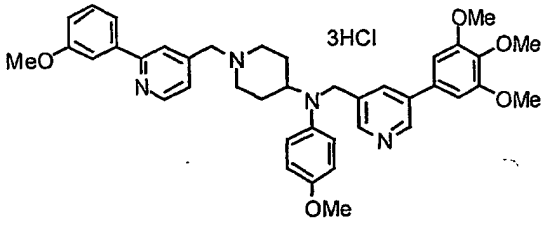
Crude 4-[N-[3-(3,4,5-trimethoxyphenyl)benzyl] -N- [4-(methylsulfonyl)phenyl] amino]piperidine and 4-chloromethyl-2-(3,4,5-trimethoxyphenyl)pylidine (29 mg) were condensed in the same manner as described in Example 9. The title compound was obtained as pale yellow powder after converting a free base to a dihydrochloride.

Yield: 23 mg (26% in 2steps).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.70-1.97 (m, 4H), 2.16-2.28 (m, 2H), 2.95-3.04 (m, 2H), 2.99 (s, 3H), 3.59 (s, 2H), 3.82 (s, 3H), 3.87-3.97 (m, 1H), 3.90 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 3.96 (s, 9H), 4.65 (s, 2H), 6.59 (s, 1H), 6.75 (d, 2H, J=9.3 Hz), 7.19-7.30 (m, 7H), 7.39 (dd, 1H, J=7.6, 7.6 Hz), 7.60 (s, 1H), 7.68 (d, 2H, J=9.0 Hz), 8.60 (d, 1H, J=4.9 Hz).

Example 204

Synthesis of 4-[N-(4-metoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3-methoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



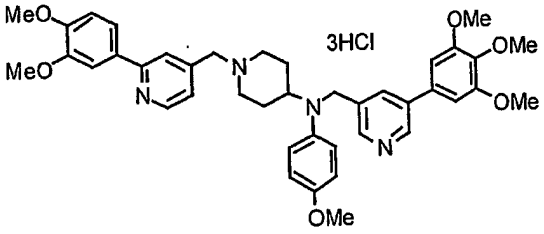
4-[N-(4-Methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride (139 mg, obtained in the Preparation Example 98) and 4-chloromethyl-2-(3-methoxyphenyl)pyridine (70 mg, obtained in the Preparation Example 195) were condensed in the same manner described in the Example 9 to give the title compound as a trihydrochloride.

Yield: 131 mg (66%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.70-1.95 (m, 4H), 2.05-2.25 (m, 2H), 2.90-3.08 (m, 2H), 3.45-3.68 (m, 3H), 3.72 (s, 3H), 3.88 (s, 3H), 3.90 (s, 9H), 4.46 (s, 2H), 6.66 (s, 2H), 6.70-6.85 (m, 4H), 6.96 (d, 1H, J=8.3 Hz), 7.21 (br, 1H), 7.38 (t, 1H, J=7.8Hz), 7.55 (t, 1H, J=7.8 Hz), 7.59 (s, 1H), 7.63-7.75 (m, 2H), 8.50 (s, 1H), 8.62 (m, 2H).

Example 205

Synthesis of 4-[N-(4-metoxyphenyl)-N-[[2-(3,4,5-trimethoxyphenyl)pyridin-4-yl]methyl]amino]-1-[[2-(3,4-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



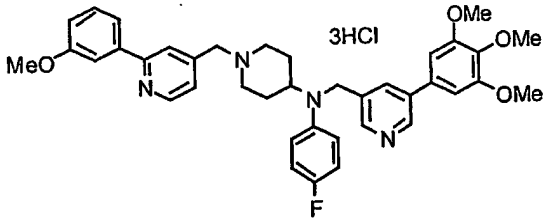
4-[N-(4-Methoxyphenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl] amino]piperidine dihydrochloride (139 mg, obtained in the Preparation Example 98) and 4-chloromethyl-2-(3,4-dimethoxyphenyl)pyridine (80 mg, obtained in the Preparation Example 197) were condensed in the same manner described in the Example 9 to give the title compound as a trihydrochloride.

Yield: 139 mg (67%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.70-1.95 (m, 4H), 2.05-2.20 (m, 2H), 2.90-3.05 (m, 2H), 3.45-3.60 (m, 3H), 3.73 (s, 3H), 3.88 (s, 3H), 3.89 (s, 6H), 3.94 (s, 3H), 4.00 (s, 3H), 4.46 (s, 2H), 6.65 (s, 2H), 6.74-6.82 (m, 4H), 6.94 (d, 1H, J=8.3 Hz), 7.15 (br, 1H), 7.52 (br, 1H), 7.58-7.71 (m, 3H), 8.50 (s, 1H), 8.57 (d, 1H, J=5.2 Hz), 8.62 (br, 1H).

Example 206

Synthesis of 4-[N-(4-fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3-methoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



4-[N-(4-Fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride (135 mg, obtained in the Preparation Example 183) and 4-chloromethyl-2-(3-methoxyphenyl)pyridine (70 mg, obtained in the Preparation Example 195) were condensed in the same manner described in the Example 9 to give the title compound as a trihydrochloride.

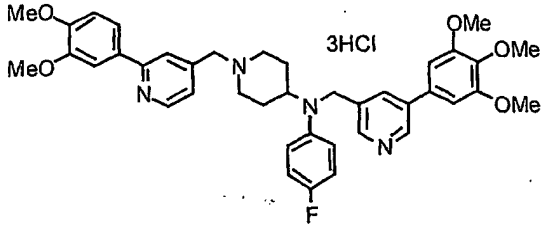
Yield: 178 mg (92%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.73-1.95 (m, 4H), 2.10-2.25

(m, 2H), 2.93-3.05 (m, 2H), 3.57 (s, 2H), 3.64 (br, 1H), 3.88 (s, 3H), 3.89 (s, 9H), 4.51 (s, 2H), 6.66 (s, 2H), 6.70-6.76 (m, 2H), 6.90 (t, 2H, J=8.3 Hz), 6.96 (d, 1H, J=8.3 Hz), 7.21 (br, 1H), 7.38 (t, 1H, J=8.0 Hz), 7.54 (d, 1H, J=7.8 Hz), 7.58 (s, 1H), 7.65 (s, 1H), 7.74 (br, 1H), 8.50 (s, 1H), 8.61 (d, 1H, J=5.1 Hz), 8.65 (br, 1H).

Example 207

Synthesis of 4-[N-(4-fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3,4-dimethoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



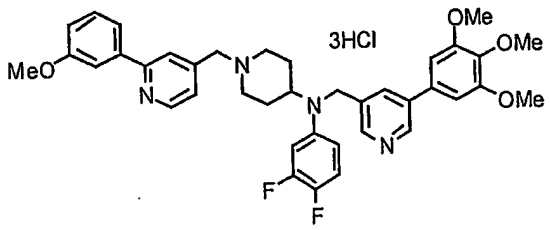
4-[N-(4-Fluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride (135 mg, obtained in the Preparation Example 183) and 4-chloromethyl-2-(3,4-dimethoxyphenyl)pyridine (80 mg, obtained in the Preparation Example 197) were condensed in the same manner described in the Example 9 to give the title compound as a trihydrochloride.

Yield: 195 mg (96%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.70-1.95 (m, 4H), 2.10-2.24 (m, 2H), 2.94-3.09 (m, 2H), 3.57 (s, 2H), 3.64 (br, 1H), 3.88 (s, 3H), 3.89 (s, 6H), 3.94 (s, 3H), 4.00 (s, 3H), 4.51 (s, 2H), 6.65 (s, 2H), 6.69-6.78 (m, 2H), 6.86-6.97 (m, 3H), 7.16 (d, 1H, J=4.9 Hz), 7.51 (d, 1H, J=8.5 Hz), 7.60-7.70 (m, 3H), 8.50 (s, 1H), 8.58 (d, 1H, J=4.9 Hz), 8.65 (s, 1H).

Example 208

Synthesis of 4-[N-(3,4-difluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]-1-[[2-(3-methoxyphenyl)pyridin-4-yl]methyl]piperidine trihydrochloride:



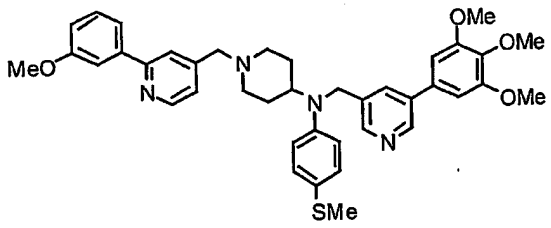
4-[N-(3,4-Difluorophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride (160 mg, obtained in the Preparation Example 176) and 4-chloromethyl-2-(3-methoxyphenyl)pyridine (80 mg, obtained in the Preparation Example 195) were condensed in the same manner described in the Example 9 to give the title compound as a trihydrochloride.

Yield: 130 mg (57%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ : 1.73-1.90 (m, 4H), 2.01-2.24 (m, 2H), 2.92-3.05 (m, 2H), 3.57 (s, 2H), 3.67 (br, 1H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s,6H), 4.52 (s, 2H), 6.36-6.42 (m, 1H), 6.50-6.58 (m, 1H), 6.67 (s, 2H), 6.93-7.01 (m, 2H), 7.20 (br, 1H), 7.38 (t, 1H, J=7.8 Hz), 7.52-7.62 (m, 2H), 7.62-7.72 (m, 2H), 8.48 (br, 1H), 8.61 (br, 1H), 8.66 (d, 1H, J=2.0 Hz).

Example 209

Synthesis of 1-[[2-(3-methoxyphenyl)pyridin-4-yl]methyl] -4-[N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]- N-(4-methylthiophenyl)amino]piperidine:



4-[N-(4-Metythiophenyl)-N-[[3-(3,4,5-trimethoxyphenyl)pyridin-5-yl]methyl]amino]piperidine dihydrochloride (121 mg, obtained in the Preparation Example 143) and 4-chloromethyl-2-(4-methoxyphenyl)pyridine (55 mg, obtained in the Preparation Example 195) were condensed in the same manner described in the Example 9 to give the title compound.

Yield: 71 mg (44%).

^{1}H-NMR (400 MHz, measured as a free base, $CDCl_3$) δ: 1.72-1.83 (m, 4H), 2.12-2.20 (m, 2H), 2.37 (s, 3H), 2.97 (d, 2H, J=10.8 Hz), 3.56 (s, 2H), 3.75-3.81 (m, 1H), 3.86 (s,

3H), 3.87 (s, 6H), 4.54 (s, 2H), 6.64-6.69 (m, 3H), 6.94 (dd, 1H, J=7.8 Hz, 1.9 Hz), 7.17-7.26 (m, 4H), 7.35 (t, 1H, J=7.8 Hz), 7.51-7.66 (m, 4H), 8.47 (s, 1H), 8.59 (d, 1H, J=4.6 Hz), 8.63 (s, 1H).

Test Example 1

Human umbilical venous endothelial cells (HUVECs) were placed in 10 cm dishes (3×10^5 cells/dish). Two days thereafter, Trichostatin A (TSA, produced by Upstate) dissolved in dimethyl sulfoxide (DMSO) and the compound prepared in Example 10 dissolved in DMSO were individually added to a final concentrations of 10 μM and 1 μM, respectively. Each sample was stimulated with TNFα (final concentration: 10 ng/mL, Genzyme -Techne). Four hours later, total RNA was extracted with ISOGEN (Nippon Gene Co., Ltd.). The subsequent procedure was performed in accordance with the manufacturer's protocol (Affymetrix). From the thus -obtained total RNA, mRNA was purified by a conventional method. cDNA was synthesized from the purified mRNA, and then biotin-labeled cRNA was synthesized by in vitro transcription. The cRNA was purified and subjected to heat treatment for fragmentation. The fragmented cRNA was used in gene expression analysis.

Method of gene expression analysis: The thus -prepared fragmented cRNA was injected to a HuGene human FL array (Affymetrix), and allowed to hybridize for 16 hours at 45°C. After washing, streptavidin labeled with phycoerythrin, and biotinylated anti -streptavidin antibody were added to each sample in order to cause reaction. Gene expression information was read by use of a dedicated scanner for GeneChip™ (Hewlett Packard). The thus -obtained information was analyzed with GeneChip Software (Affymetrix) for comparison in terms of level of expression.

The mRNA expression levels of 52 genes were twice or more increased by stimulation with TNFα. As shown in Fig. 1, the mRNA expression levels of these genes under addition of TSA and those under addition of the compound prepared in Example 10 have a positive correlation. In 25 genes (including VCAM -1, fractalkine, lymphotoxin β, and RDC -1) out of these genes, expression was inhibited by TSA and also by the compound prepared in Example 10. Conversely, expression was enhanced in 6 genes (including ICAM -1). The above results demonstrate that TSA and the compound prepared in Example 10 have similar actions on TNFα -stimulated HUVECs.

Table 1

Genes with suppressed expression in the presence of the two agents

Genes	No stimula -tion	TNFα stimulation	+ Compound of Example 10	+ TSA
OB -cadherin -2	47	97	24	62
caspase -like apoptosis regulatory protein 2 (clarp)	86	245	76	50
Nef associated factor 1	241	844	496	396
M -Ras -regulated GEF	46	119	37	39
Spliceosomal Protein Sap 49	37	96	40	79
ets -2	33	140	90	38
cytoplasmic antiproteinase 2 (CAP2)	60	142	78	37
MCP -1	41	151	43	46
IL -7R	49	143	44	44
VCAM -1	18	873	83	96
EphrinA1	96	356	148	113
p50 -NF -kappa B homolog	5	158	33	57
Cox -2	22	154	0	30
BCL3	114	283	125	198
IFNGR2	59	418	186	209
Na/K -ATPase beta -1	87	200	78	148
TRAF1	46	600	88	262
IAP homolog B	68	177	42	99
RDC1	8	293	27	21
ninjurin1	104	182	135	150
fractalkine	-15	433	7	38
lymphotoxin beta	-78	258	-56	-40
metalloproteinase stromelysin -2	45	98	54	69
ABC transporter B2	37	185	69	66
beta -galactoside alpha -2;6 -sialyltransferase	27	96	14	19

Genes with enhanced expression in the presence of the two agents

Genes	No stimula -tion	TNFα stimula -tion	+ Compound of Ex. 10	+ TSA
ICAM -1	-19	1601	2174	2303
I kappa B alpha	271	1174	1259	1363
B94	5	610	1010	924
junB	5	99	210	123
exodus -1	-19	157	310	1206
Gro1	131	466	614	855

Test Example 2

TSA (final concentration: 10 μM) or the compound prepared in Example 10 (final concentration: 1 μM) was added to HUVECs. The samples were stimulated with TNFα (final concentration: 10 ng/mL) for five hours, and RNA was recovered by use of an RNeasy Mini Kit (QIAGEN) in accordance with the manufacturer's protocol. Subsequently, cDNA was synthesized from the recovered RNA through a conventional method. The cDNA was subjected to quantitative PCR by the TaqMan probe method with a real -time quantitative PCR apparatus (ABI PRISM 7900HT, Applied Biosystems). The assay was performed for VCAM -1, GM -CSF, fractalkine, and ICAM -1. The expression level without stimulation was subtracted from the expression level with stimulation of TNFα, and assuming the resulting value to be 100, relative expression level was calculated. The results are shown in Fig. 2. TSA and the compound prepared in Example 10 exhibited either inhibitory or enhancing action on gene expressions. The results support the analysis results obtained from the test using GeneChip (see Test Example 1).

Test Example 3

Cultured human cancer cells were placed in a 96 -well plate. On the following day, a solution of the compound prepared in Example 10 (in five concentrations resulting from 10 -fold stepwise dilution: 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, or 10^{-8} M) was added, followed by incubation for two days. Cell count after growth was determined in each plate through colorimetry using sulforhodamine B. The concentration at which the cell count after growth was inhibited to 50% of that of the cell count of the control (in the absence of the compound prepared in Example 10) was calculated (GI50). Simultaneously, on the basis of the cell count just before addition of the compound prepared in Example 10 (time zero), the following value (concentration) was calculated.

TGI: a concentration at which cell growth is inhibited to a cell count equal to that at time zero (concentration at which no change in cell count is observed)

LC50: a concentration at which cell count is reduced to 50% of the cell count at time zero (cell -killing effect).

Table 2 shows the growth inhibitory effect of the compound prepared in Example 10 on 9 typical cancer cells.

Table 2

Cancer cell lines	GI50 (μM)	TGI (μM)	LC50 (μM)
MCF -7 (breast cancer)	0.16	>100	>100
SF -539 (brain tumor)	0.83	>100	>100
HCC2998 (colon cancer)	0.33	10	40
DMS114 (lung cancer)	0.038	2.6	>100
LOX -IMVI (melanoma)	0.18	1.2	41
OVCAR -3 (ovarian cancer)	0.35	39	>100
ACHN (renal cancer)	1.9	>100	>100
MKN74 (stomach cancer)	0.026	0.56	>100
PC -3 (prostatic carcinoma)	26.3	>100	>100

As is apparent from Table 2, the compound prepared in Example 10 exhibits strong growth inhibitory effect (GI50) on typical cultured human cancer cells. Moreover, LC50 values suggest that the compound produces reduced side effects.

Test Example 4

Cultured human cancer cells were added to a 96 -well plate. On the following day, a solution of each of the compounds prepared in Examples 13, 23, 29, 36, and 114 (in five concentrations resulting from 10 -fold stepwise dilution: 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, or 10^{-8} M) was added, followed by incubation for 48 hours. Subsequently, %growth of the cells was measured through colorimetry by use of a WST-1 (Dojindo) reagent for measurement of cell count. From the measurement data, % growth was calculated by use of the following equation, and 50% growth inhibitory concentration (GI50) was calculated from the dose -response curve of each compound:

% growth = {[(OD as measured after 48 hours from addition of compound) - (OD at time zero)]/[(OD of control as measured after 48 hours) - (OD at time zero)]} × 100.

As is apparent from Table 3, the compounds prepared in Examples 13, 23, 29, 36, and 114 all exhibited strong growth inhibitory effect on cultured human cancer cells.

Table 3

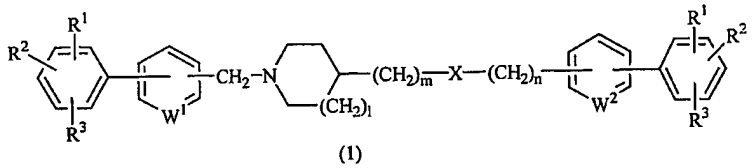
Compound (Example No.)	MCF -7 (breast cancer) [GI50 (μM)]	HCT -15 (colon cancer) [GI50 (μM)]	MKN -45 (stomach cancer) [GI50 (μM)]	MKN -74 (stomach cancer) [GI50 (μM)]
13	0.7	0.8	3	0.7
23	0.6	0.9	4	0.7
29	0.7	0.8	3	0.4
36	0.7	1	2	0.6
114	0.6	0.8	2	0.2

Industrial Applicability

The present invention can provide a method for treating cancer with reduced side effects.

Claims

1. A histone deacetylase inhibitor comprising a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof.

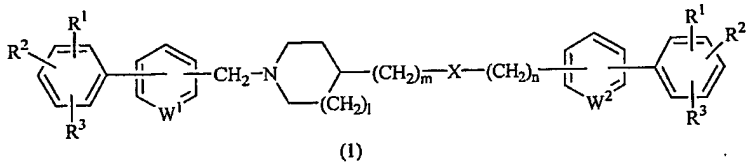
2. The inhibitor according to claim 1, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxyl group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

3. The inhibitor according to claim 1, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

4. The inhibitor according to claim 3, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is (are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

5. The inhibitor according to claim 1, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

6. A medicine for treating cancer comprising a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof.

7. The medicine according to claim 6, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

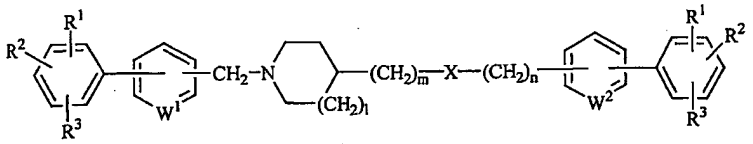
8. The medicine according to claim 6, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or

unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

9. The medicine according to claim 8, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

10. The medicine according to claim 6, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

11. A gene therapy facilitater comprising administering an effective amount of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl

group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0or 1), a salt thereof, or a solvate thereof.

12. The facilitater according to claim 11, wherein R^1, R^2, and R^3 each are independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

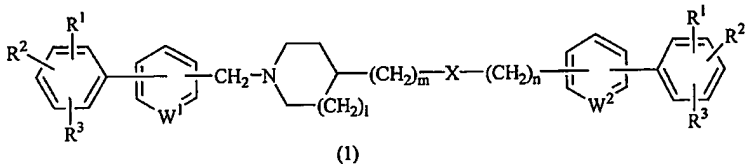
13. The facilitater according to claim 11, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

14. The facilitater according to claim 13, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

15. The facilitater according to claim 11, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

16. A histone deacetylase inhibiting composition comprising a cyclic amine

compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

17. The composition according to claim 16, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxyl group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

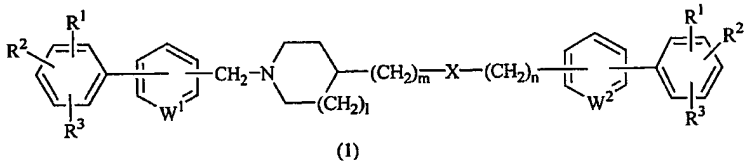
18. The composition according to claim 16, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

19. The composition according to claim 18, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is (are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

20. The composition according to claim 16, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4

-[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

21. A medicinal composition for treating cancer comprising a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

22. The composition according to claim 21, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

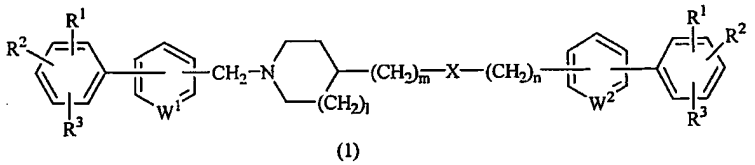
23. The composition according to claim 21, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted

heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

24. The composition according to claim 23, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

25. The composition according to claim 21, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

26. A gene therapy facilitating composition comprising a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0or 1), a salt thereof, or a solvate thereof, and a pharmaceutically acceptable carrier.

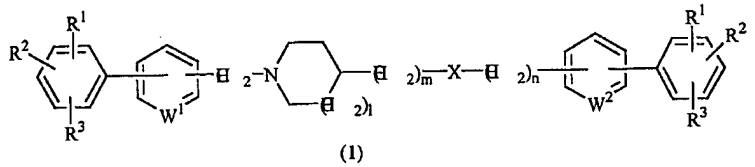
27. The composition according to claim 26, wherein R^1, R^2, and R^3 each are independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

28. The composition according to claim 26, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

29. The composition according to claim 28, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

30. The composition according to claim 26, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

31. Use, for producing histone deacetylase inhibitor of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof.

32. The use according to claim 31, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxyl group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

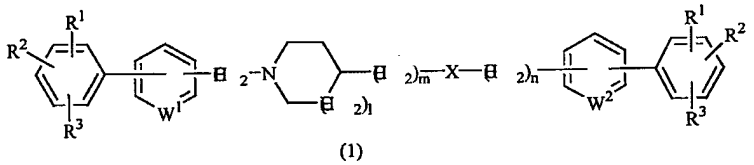
33. The use according to claim 31, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

34. The use according to claim 33, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is (are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

35. The use according to claim 31, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5

-trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

36. Use, for producing medicine for treating cancer of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof.

37. The use according to claim 36, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

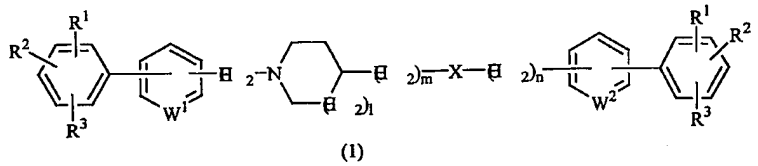
38. The use according to claim 36, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to

four nitrogen atoms.

39. The use according to claim 38, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

40. The use according to claim 36, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

41. Use, for producing gene therapy facilitator, of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0or 1), a salt thereof, or a solvate thereof.

42. The use according to claim 41, wherein R^1, R^2, and R^3 each are

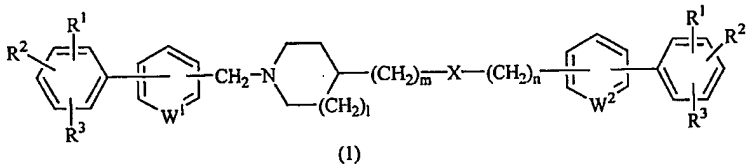
independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

43. The use according to claim 41, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

44. The use according to claim 43, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

45. The use according to claim 41, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

46. A method for inhibiting histone deacetylase, comprising administering an effective amount of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof.

47. The method according to claim 46, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxyl group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

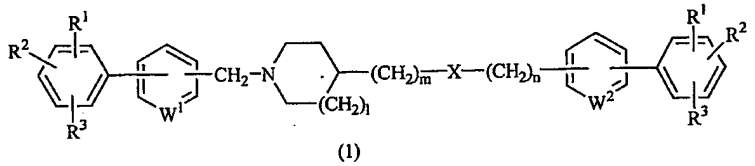
48. The method according to claim 46, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

49. The method according to claim 48, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is (are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

50. The method according to claim 46, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2

-(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

51. A method for treating cancer, comprising administering an effective amount of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0 or 1), a salt thereof, or a solvate thereof.

52. The method according to claim 51, wherein R^1, R^2, and R^3 are each independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

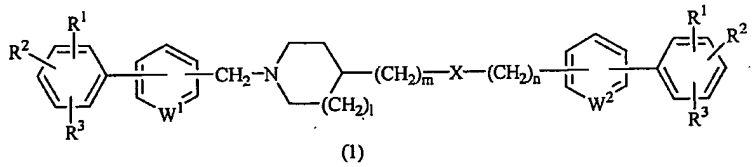
53. The method according to claim 51, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to

four nitrogen atoms.

54. The method according to claim 53, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

55. The method according to claim 51, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

56. A method for facilitating gene therapy, comprising administering an effective amount of a cyclic amine compound represented by the following formula (1):



(1)

(wherein R^1, R^2, and R^3 each independently represent a hydrogen atom, a halogen atom, a hydroxy group, an alkyl group, a halogen -substituted alkyl group, an alkoxy group, an alkylthio group, a carboxyl group, an alkoxycarbonyl group, or an alkanoyl group; W^1 and W^2 each independently represent N or CH; X represents O, NR^4, $CONR^4$, or NR^4CO; R^4 represents a hydrogen atom, an alkyl group, an alkenyl group, an alkynyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted heteroaralkyl group; and l, m, and n each represent a number of 0or 1), a salt thereof, or a solvate thereof.

57. The method according to claim 56, wherein R^1, R^2, and R^3 each are

independently a hydrogen atom, a halogen atom, a hydroxy group, a C1 -C8 alkyl group, a halogen -substituted C1 -C8 alkyl group, an alkoxy group having a C1 -C8 alkyl group, an alkylthio group having a C1 -C8 alkyl group, a carboxy group, an alkoxycarbonyl group having a C1 -C6 alkyl group, or an alkanoyl group having a C1 -C6 alkyl group.

58. The method according to claim 56, wherein R^4 is a hydrogen atom, a C1 -C8 alkyl group, a C3 -C8 alkenyl group, a C3 -C8 alkynyl group, a substituted or unsubstituted C6 -C14 aryl group, a substituted or unsubstituted heteroaryl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms, a substituted or unsubstituted (C6 -C14) -aryl -(C1 -C6) -alkyl group, or a substituted or unsubstituted heteroaryl -(C1 -C6) -alkyl group containing a 5 - or 6 -membered ring having one to four nitrogen atoms.

59. The method according to claim 58, wherein the substituent(s) of the aryl group, the aryl group of the aralkyl group, the heteroaryl group, or the heteroaryl group of the heteroaralkyl group represented by R^4 is(are) one to three groups or atoms selected from an alkyl group, an alkoxy group, an alkylthio group, a halogen atom, a nitro group, an amino group, an acetylamino group, a trifluoromethyl group, and an alkylenedioxy group.

60. The method according to claim 56, wherein the active ingredient is 4 -[N -(4 -methoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methoxyphenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,5 -dimethoxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(3,4 -methylenedioxyphenyl) -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -methyl -N -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, 4 -[N -(4 -methylthiophenyl) -N -[[5 -(3,4,5 -trimethoxyphenyl)pyridin -3 -yl]methyl]amino] -1 -[[2 -(3,4,5 -trimethoxyphenyl)pyridin -4 -yl]methyl]piperidine, or a salt thereof.

Fig. 1

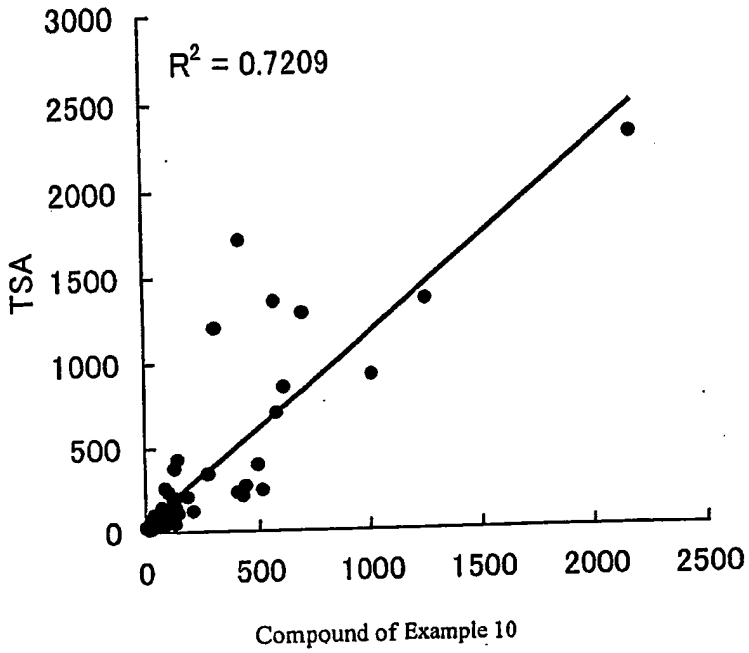
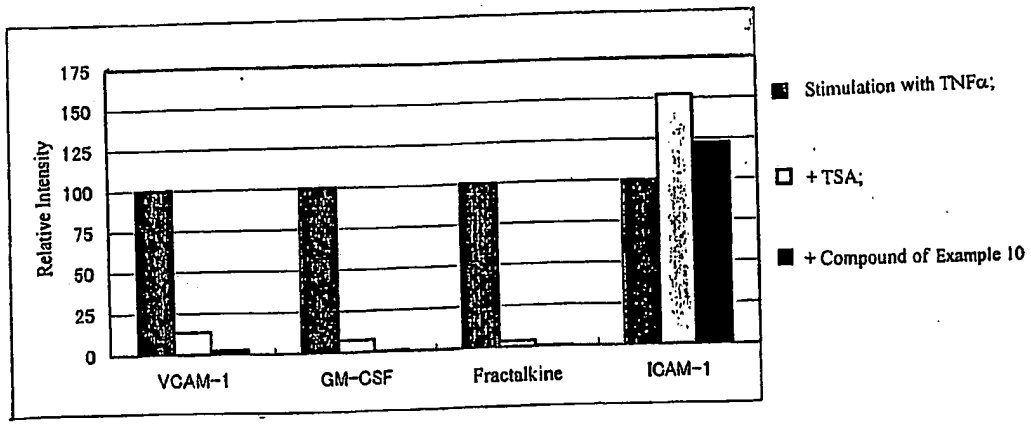

3000
2500
2000
1500
1000
500
0
TSA
R^2 = 0.7209
0
500
1000
1500
2000
2500
Compound of Example 10

Fig. 2


175
150
125
100
75
50
25
0
Relative Intensity
VCAM-1
GM-CSF
Fractalkine
ICAM-1
Stimulation with TNFα;
+TSA;
+ Compound of Example 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/04602

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] A61K31/4545,31/4468,A61P35/00,C07D401/14,401/06,405/14,401/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] A61K31/4545,31/4468,A61P35/00,C07D401/14,401/06,405/14,401/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Japanese Utility Model Gazette 1926-1996, Japanese Publication of Unexamined Utility Model Applications 1971-2001, Japanese Registered Utility Model Gazette 1994-2001, Japanese Gazette Containing the Utility Model 1996-2001

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN),REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PA	US 6395753 B1(KOWA CO.,LTD) 2002.05.28,Whole document,(Family:none)	1-45
A	EP 0774257 A2(KOWA CO.,LTD) 1997.05.21,Claims1-10,Page2 Line7-10 & JP 09-143075 A	1-45

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21.05.03	10.06.03

Name and mailing address of the ISA/JP	Authorized officer	
Japan Patent Office 3-4-3, Kasumigaseki, Chiyoda-ku, Tokyo 100-8915, Japan	KIMITAKA MURAKAMI (Seal) Telephone No. +81-3-3581-1101 Ext. 3452	4C 3229

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP03/04602

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: 46-60
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claims 46-60 relates to a method for treatment of the human body by therapy, which does not require an intentional search by the International Searching Authority in accordance with PCT Article 17(2)(a)(i) and [Rule 39.1(iv)].

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.